Collective Expert Report

Cancer

A methodological approach for studying the link between cancer and the environment

Summary

Inserm
Institut national de la santé et de la recherche médicale
(National Institute for health and medical research)
2004

This document presents the results of work of the expert group convened by Inserm through the collective expert evaluation procedure to answer the questions raised by the French Agency for Environmental Safety and Health (*Agence française de sécurité sanitaire environnementale* - Afsse).

The expertise is based on available scientific data taken from about 200 relevant articles and documents from the last semester of 2004.

The Inserm Collective Expertise Center co-ordinated this collective work with the Department for Facilitation and Scientific Partnership (*Département animation et partenariat scientifique* - Daps) to instruct the dossier and with the information resources services of the Department of Scientific Information and Communication (*Département de l'information scientifique et de la communication* - Disc) for bibliographic research.

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Foreword

In spite of the wealth of cancer research endeavors over the last decades, cancer incidence and mortality have not receded at the same rate as that for other pathologies. Primary prevention therefore remains the most pertinent approach for reducing cancer incidence and hence mortality.

It is generally recognized that environmental exposure is involved with varying degrees in the etiology of most cancers. Some believe that half of cancer cases could be avoided by applying existing etiological knowledge. However, this estimate is widely debated for lack of consensus criteria among the scientific community.

In this context, Afsse[1] has entrusted Inserm with a collective expertise to identify cancers exhibiting an incidence increase in France that is not only the result of improvement in diagnostic criteria and techniques or screening strategies. In order to evaluate the possible role of environmental risk factors, it is necessary to define a methodological approach to look for etiological links between exposure to one or more environmental factors and the occurrence of various cancers, as well as the conditions required to quantify the risk attributable to such factors.

In this first expertise endeavor, the group of experts has addressed the issue by tackling the following questions:

- What are the adult and child cancers for which incidence and mortality in France increase?
- What is France's position relative to other European countries in terms of mortality per cancer category?
- What epidemiological approaches can be used to look for causal links between exposure factors and cancer?
- To what extent have experimental studies contributed to establish the biological plausibility of a causal relationship between exposure factors and cancer?
- What is the contribution of genetic susceptibility factors in the causal relationship?
- Which models can be used to study the effects of multiple low-dose exposures?
- What methods can be used to estimate the risk attributable to various environmental factors?

In the course of four work sessions, the experts analyzed relevant international literature and data concerning the French population and have as a result built a report divided into eight chapters.

On the basis of the methodological approach defined in this first expertise, it has been agreed that Afsse will entrust Inserm with several thematic expertise missions in order to draw up a status report on knowledge about the environmental factors that might contribute to the rise in incidence of cancers of interest, whether such factors are generally present in the environment or only in the workplace. Such knowledge is likely to help define appropriate public actions that should be undertaken to prevent environmental risks.

[1] French Agency for Environmental Safety and Health (Agence française de sécurité sanitaire environnementale)

I

Epidemiological data

Introduction

The rise in cancer incidence in France between 1980 and 2000 has been estimated at around 60%. This increase is partly due to population ageing but there remains a 30% increase in the rate of cancer incidence after normalizing for age. Several factors can explain this increase: better diagnosis, more efficient population surveillance and greater susceptibility to develop the disease. In order to understand the evolution of the rise in cancer cases and analyze the individual influence of the various factors, it is essential to observe the trend of incidence in terms of cancer localization.

European data from the ACCIS database (Automated Childhood Cancer Information System) indicate there has been a rise in cancer incidence for children and adolescents since the 70's together with an acceleration of this trend. American data also report a rise in child cancer incidence similar to that observed in adults (around 25%) beginning in 1975, with a leveling-off since 1990. The data available from regional registers in France for the period 1990-1999 do not show evidence of a rise in pediatric cancer incidence.

In the European population, approximately 1% of cancers patients are under 20. This relatively low frequency makes it difficult to study risk factors. The problem is compounded by the fact that many types of tumors are children-specific.

At the break of the 21st century, cancers in France constitute the first cause of mortality among the male population, and the second cause of mortality among the female population after cardiovascular disease. Lung and breast cancers are the leading causes of death in men and women respectively.

Analyzing data on cancer mortality in the European Union (EU) provides a basis for assessing France's specific situation. Thus, for all cancers irrespective of localization, the male cancer death rate is higher in France than it is in other European countries. Lung cancer contributes by about 30% to the total male cancer mortality in Europe. Analyzing European data should also "indirectly" reveal the disparities in risk factors and prevention measures.

1

Incidence and evolution of adult cancers in France

Given the absence of observational data on incidence of adult cancers in France, evolution of the number of cancer cases across the country can only be estimated.

Numbers were estimated on the basis of available mortality data for the whole of France and the incidence data obtainable from French departments covered by a cancer register. The case collection methodology used by cancer registers, the statistics methodology and all the results used to make the estimate are described in detail in the publication emanating from the network of French cancer registers, FRANCIM, and the National Institute for Public Health (InVS)[2] (Remontet et al., 2002).

The main hypothesis on which this estimate is based is that the mortality/incidence ratio for one sex, one age group and a given cohort remains constant whether or not French departments are covered by a cancer register.

Evolution of cancer frequency over the last 20 years

Between 1980 and 2000, the annual number of new cancer cases in France has gone up from 170,000 to 278,000 (63%), the rise being slightly more pronounced in men (97,000 to 161,000; 66%) than women (73,000 to 117,000; 60%) (Table 1.I).

Table 1.I: Increase in the number of cancer cases in France

	1980	2000	Increase
Men	97,000	161,000	+66%
Women	73,000	117,000	+60%
Men and Women	170,000	278,000	+63%

It is estimated that 45% of the rise in the number of cases are due to French society's demographic evolution (population growth and ageing) and 55% to an increase in the frequency (incidence) of cancers for each age group (Figure 1.1).

The rise in incidence varies according to cancer localization. The publication by Remontet et al. (2002) gives the mean annual evolution rate (%) of the age-standardized incidence of each cancer localization between 1978 and 2000. The following bar graphs (Figures 1.2 and 1.3) show the cancer localizations for each sex with a rise in annual incidence rate greater than or equal to 1% by order of decreasing incidence rise.

[2] Institut de Veille Sanitaire

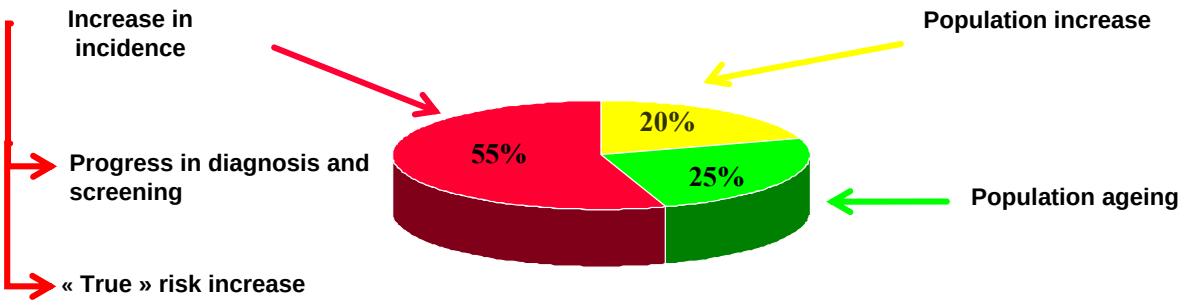

Figure 1.1: Distribution of causes of increase in the number of cancer cases in France (from Remontet et al., 2002)

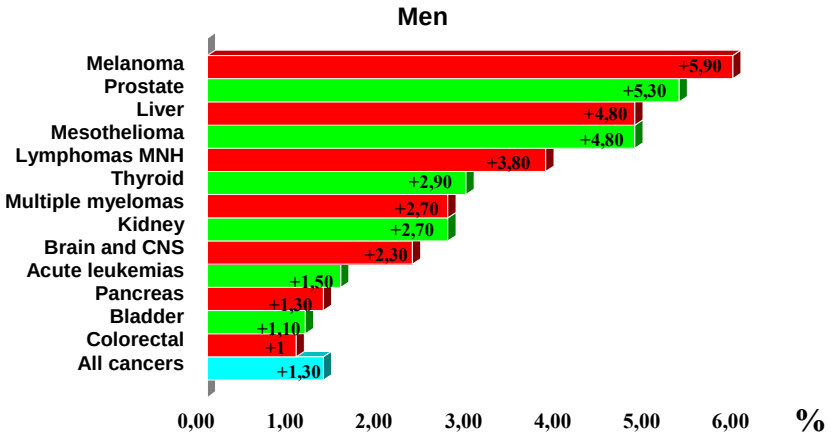

Figure 1.2: Mean annual rate of increase in the incidence of male cancers in France (1978-2000) (≥1%)

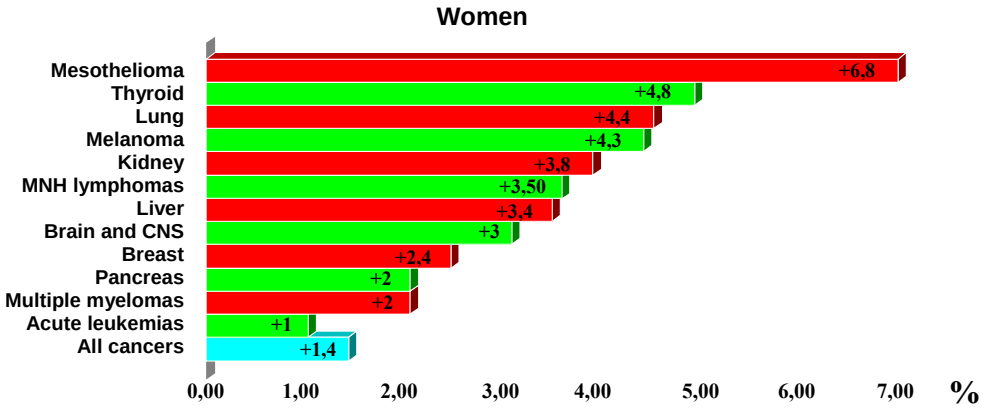

Figure 1.3: Mean annual rate of increase in the incidence of female cancers in France (1978-2000) (≥1%)

In men, the five cancers that show the most marked incidence increase between 1978 and 2000 are skin melanoma, prostate cancer, liver cancer, pleural mesothelioma, and malignant non-Hodgkin's lymphoma. In women, they are pleural mesothelioma, thyroid cancer, lung cancer, skin melanoma and renal cancer.

In terms of public health, estimating the relative weight of a given cancer localization requires that one also consider the mean annual incidence level. Thus, for example, a 10% annual increase in mesothelioma incidence would lead to the appearance of about 100 new cases each year while a three-fold lower increase in lung cancer would lead to the appearance of 1,000 new cancer cases.

Aside from the criterion of annual variation percentage, it is interesting to consider a criterion that combines mean frequency and level of increase. Table 1.II shows a ranking of the 15 cancers with the highest mean annual number of new cases (with a threshold of 30) in France from 1980 to 2000.

Table 1.II: Cancers with the highest mean annual number of new cases in France between 1978 and 2000

Localization	Annual Variation (%)		Annual variation (number of new cases due to incidence increase)
	Men	Women	
Prostate	+5.33		2,150
Breast		+2.42	1,010
MNH lymphomas	+3.82	+3.46	360
Skin melanoma	+5.93	+4.33	360
Colorectal	+0.99	+0.83	330
Lung	+0.58	+4.36	330
Liver	+4.8	+3.38	270
Kidney	+2.70	+3.74	250
Thyroid	+2.89	+4.80	170
Brain and CNS	+2.25	+ 3.01	140
Bladder	+1.14	-0.50	90
Pancreas	+1.27	+2.07	80
Multiple myeloma	+2.65	+1.96	80
Mesothelioma	+4.76	+6.83	50
Acute leukemia	+1.48	+0.92	30

Judging from the mean annual number of new cases due to incidence increase, the two predominant localizations are prostate and breast cancer, which alone represent over 50% of the new cancer cases due to a rise in incidence (Figure 1.4). While exhibiting one of the highest relative increases, mesothelioma only ranks 14 in order of importance by this particular criterion.

The choice of criterion to classify cancers as a function of their evolution over the last 20 years depends entirely on the nature of the question to be addressed. Should one wish to focus on the quantitative aspect, the criterion that combines mean incidence level and relative annual variation seems to be the most appropriate.

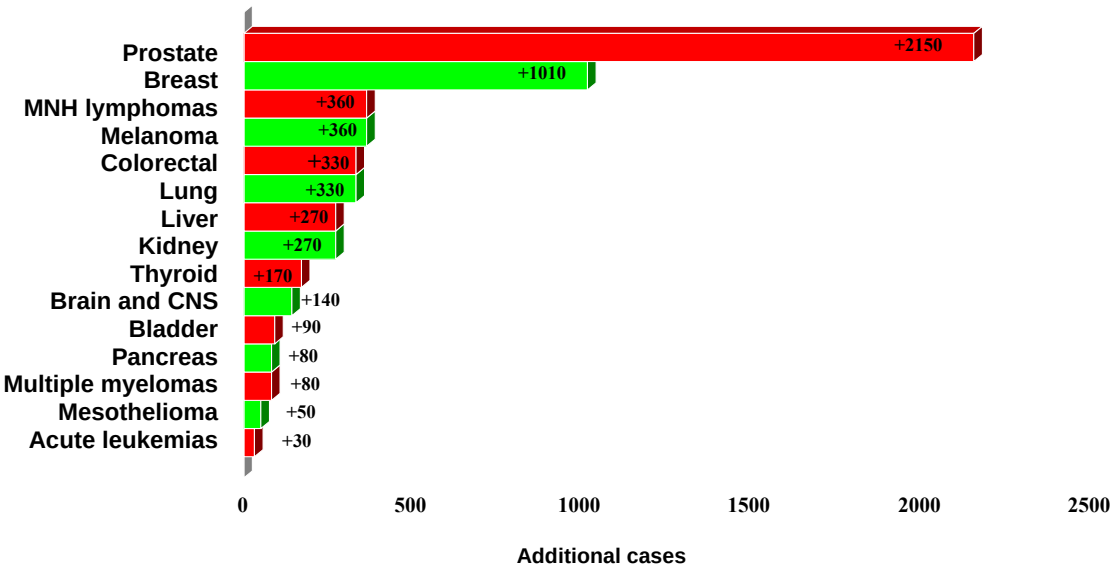

Figure 1.4: Annual increase in the number of cancers in France between 1978 and 2000

Identification of cancers exhibiting an incidence and mortality increase

Table 1.III shows cancers exhibiting an incidence increase that contributes very significantly to the rise in total cancer (in decreasing order).

The table also shows whether these cancers are not only on the increase but also exhibit a concomitant increase in mortality. A rise in incidence without a parallel increase in mortality can be explained at least in part by modifications in health care practice (screening and diagnosis). Indeed, one might suppose that incidence increase is essentially due to cancers with better prognosis particularly as a result of improved screening procedures and earlier diagnosis. A rise in incidence without an increase in mortality could also be explained by substantial therapeutic progress for particular cancer localizations.

Finally, one might suppose that a joint increase in incidence and mortality reflects a risk increase linked to the fact that the prevalence of risk factors is on the rise or rose over a time period compatible with the latency period of the cancers involved. Such factors may be linked with individual behavior (sedentarity, alcohol, active smoking, sun exposure…) and environmental factors (occupational exposure, passive smoking, and atmospheric, earth or water pollution…).

Table 1.III: Increase in cancer number, incidence and mortality between 1980 and 2000 (from Remontet et al., 2002)

Localization	Rise in number	Rise in incidence and mortality
Prostate	2.150	NO
Breast	1.010	NO
MNH lymphomas	360	YES
Skin melanoma	360	NO
Colorectal	330	NO
Lung	330	YES
Liver	270	YES (in men)

Kidney	250	NO
Thyroid	170	NO
Brain and CNS	140	YES
Bladder	90	NO
Pancreas	80	YES
Multiple myelomas	80	NO
Mesothelioma	50	YES
Acute leukemia	30	NO

Table 1.IV presents cancers exhibiting a parallel increase in incidence and mortality in France, in decreasing order of incidence.

Table 1.IV: Cancers exhibiting a parallel increase in incidence and mortality in France between 1980 and 2000, in decreasing order of incidence

Localization	Incidence in 2000	Mortality in 2000	Rise in incidence in numbers/year	Rise in mortality in numbers/year
Lung	27.743	27.164	334	281
Malignant hemopathies (adults)*	17.468	9.943	461	227
Liver	5.976	7.850	275	226
Brain/CNS (adults)	5.300	3.168	140	76
Pancreas	4.887	7.181	80	68
Pleural mesothelioma	871	1.157	46	27

* Including MNH lymphomas; multiple myelomas; Hodgkin's disease; acute leukemia

In conclusion, among cancers that show a rise in incidence, only non-Hodgkin malignant lymphomas, lung cancers, liver cancers, brain and CNS cancers, pancreatic cancers and pleural mesothelioma have presented a parallel rise in mortality over the last twenty years.

The incidence increase for breast and prostate cancers represents more than 50% of the annual rise in cancers and do not exhibit a parallel evolution of incidence and mortality. Not surprisingly, both are cancers for which there has been a progressive development of screening over the last twenty years.

REFERENCES

REMONTET L, BUEMI M, VELTEN M, JOUGLA E, ESTEVE J. Évolution de l'incidence et de la mortalité par cancer en France de 1978 à 2000. Éditions InVS, 2002 : 217p

2

Mortality by cancer in the European Union – The situation in France

The greater availability of indicators on the causes of death in Europe and the progressive standardization of methods to obtain data have allowed increasingly reliable comparative analyses of the mortality levels in countries of the European Union (Jougla and Pavillon, 1997; Jougla et al., 1998). Regarding cancer, this type of study is turning out to be very efficient to demonstrate by indirect means the disparity in risk factors and prevention practices. The aim of this chapter is to analyze the weight of mortality by cancer in the European Union (EU) as well as characterize the situation in France (Jougla et al., 2003)[3].

The analysis is based on mortality data in 1999 in the EU (15 members)[4], published by Eurostat in the form of a succinct list of initial causes of death (comprising 18 cancer sub-categories). The indicators used are numbers of deaths, standardized death rates according to EU age structure (all ages and under 65) and mortality ratios between sexes. Short-term evolution (1994-1999) is also analyzed.

Cancer and causes of premature deaths in the European Union

Deaths by cancer represent a quarter of the total number of deaths that occur annually in the fifteen EU member countries (960.000 deaths by cancer per year). In the case of premature deaths (under 65), the proportion is as high as 37% (261.000 deaths) with cancer representing the first cause of death, ahead of cardiovascular mortality. For men (534.000 deaths by cancer), lung cancer represents 28% of total cancer mortality, followed by cancers of the intestine (11%) and prostate (10%). For women, breast cancer is predominant (one death out of five) ahead of cancer of the intestine (12%) and lung cancer (11%).

For most cancer localizations, a general improvement in mortality levels in the EU from 1994 to 1999 has been observed (Tables 2.I and 2.II). The most significant progress is seen for cancers of the stomach (both sexes), of the bladder and kidney (men), and of the uterus. Conversely, the frequency of occurrence of certain localizations is unchanged: pancreas, liver, lymphomas and leukemia (both sexes) and upper respiratory tract (women). European death levels have risen for two cancer localizations: lung cancer in women and skin melanoma in men. The decrease in death rate for men under 65 has been slightly more pronounced, irrespective of anatomic site, than for the population in general. In the case of women, the reduction in death rate is of a similar order for both premature deaths and total deaths. There is, however, a strong progression of female mortality under 65 by cancer of the lung and upper aero-digestive tract (UADT).

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3 We thank the Bulletin Épidémiologique Hebdomadaire for authorizing the use of the article : JOUGLA E, SALEM G, RICAN S, PAVILLON G, LEFEVRE H. Disparités de la mortalité par cancer dans l'Union européenne. *BEH* 2003, 41-42 : 198-201

4 For data concerning the 25-member European Union, see Boyle and Ferlay, 2005.

Table 2.I: Death rate by cancer in the European Union and in France[1], male

	All ages					< 65 years				
	EU 1999	Fr 1999	Fr/EU 1999	Var[2] 94/99 EU	Var[2] 94/99 Fr	EU 1999	Fr 1999	Fr/EU 1999	Var[2] 94/99 EU	Var[2] 94/99 Fr
Lung	70.9	74.4	1.05	-9%	-4%	29.4	38.6	1.31	-11%	-4%
Colorectal	26.8	26.9	1.00	-4%	-1%	8.4	7.7	0,92	-6%	-4%
Prostate	25.7	27.8	1.08	-7%	-7%	2.5	2.5	1.00	-7%	-14%
Hemolymphatic tissues	18.2	19.2	1.05	-1%	-1%	7.4	7.5	1.01	-5%	-1%
UADT	16.3	26.2	1.61	-7%	-13%	9.8	17.3	1.77	-8%	-13%
Bladder-Kidney	15.9	16.9	1.06	-11%	-3%	4.4	5.4	1.23	-15%	-5%
Stomach	14.8	10.2	0.69	-19%	-15%	5.0	3.5	0.70	-17%	-5%
Pancreas	11.0	11.7	1.06	-1%	+2%	4.5	4.9	1.09	0%	+2%
Liver	10.8	16.7	1.55	-1%	-2%	4.0	6.5	1.63	-5%	-3%
Skin melanoma	2.4	2.2	0.92	+4%	+5%	1.4	1.4	1.00	0%	+8%
Others	41.5	51.1	1.23	-3%	-9%	17.5	24.3	1.39	-5%	-10%
Total	254.3	283.3	1.11	-7%	-6%	94.3	119.6	1.27	-8%	-6%

[1] EU age-standardized rate per 100 000 population; [2] (1999 rate – 1994 rate) / (1994 rate)

Table 2.II: Death rate by cancer in the European Union and in France [1], female

	All ages					< 65 years				
	EU 1999	Fr 1999	Fr/EU 1999	Var[2] 94/99 EU	Var[2] 94/99 Fr	EU 1999	Fr 1999	Fr/EU 1999	Var[2] 94/99 EU	Var[2] 94/99 Fr
Breast	27.9	28.5	1.02	-9%	0%	17.2	18.0	1.05	-10%	+1%
Colorectal	16.8	15.2	0.90	-8%	-4%	5.6	4.9	0.88	-7%	-4%
Lung	15.8	11.3	0.72	+5%	+26%	7.7	6.6	0.86	+10%	+38%
Hemolymphatic tissues	11.8	11.7	0.99	+1%	-1%	5.0	4.5	0.90	-4%	-8%
Ovary	8.3	7.9	0.95	-7%	-2%	4.5	4.1	0.91	-8%	-5%
Pancreas	7.5	6.9	0.92	+1%	+10%	2.5	2.5	1.00	0%	+19%
Stomach	6.9	4.0	0.58	-19%	-15%	2.4	1.3	0.54	-14%	+8%
Uterus	6.7	7.0	1.04	-13%	-9%	3.6	3.5	0.97	-12%	-15%
Bladder-Kidney	4.9	4.7	0.96	-6%	+2%	1.5	1.4	0.93	-6%	0%
Liver	3.8	3.4	0.89	-3%	+3%	1.2	1.2	1.00	0%	0%
UADT	3.6	3.5	0.97	0%	+3%	1.8	2.1	1.17	+13%	+5%
Skin melanoma	1.6	1.6	1.00	-6%	0%	1.0	1.0	1.00	-9%	0%
Others	27.3	25.7	0.94	-5%	-9%	10.6	10.5	0.99	-9%	-7%
Total	142.9	131.4	0.92	-5%	-1%	64.6	61.6	0.95	-6%	+1%

[1] EU age-standardized rate per 100.000 population; [2] (1999 rate - 1994 rate) / (1994 rate)

Death rate by cancer in France relative to the European Union

A strong disparity in levels of mortality by cancer can be observed overall and according to cancer type between countries of the European Union (Table 2.III).

Cancer mortality in men

France has the highest male death rate for cancer, followed by Belgium and the Netherlands. The lowest death rates are found in Sweden, Finland and Greece. Thus for instance, the death rate is 50% and 20% higher in France than it is in Sweden and the United Kingdom respectively.

Table 2.III: Standardized death rates by cancer in EU countries[1], male; all ages

	Total		Lung		Colorectal		UADT		Liver	
	1999	var/94 [2]	1999	var/94	1999	var/94	1999	var/94	1999	var/94
France	283.3	-6%	74.4	-4%	26.9	-1%	26.2	-13%	16.7	-2%
Belgium[3]	282.5		102.9		26.9		16.5		6.6	
Netherlands	275.8	-5%	86.2	-13%	28.5	+1%	14.8	+10%	3.9	+86%
Spain	265.1	-1%	79.3	-2%	27.6	+10%	16.3	-9%	12.3	-1%
Denmark[3]	262.1		72.0		33.5		15.2		5.1	
Italy	260.3	-7%	78.4	-9%	24.3	-4%	11.6	-14%	18.4	-10%
Ireland	252.5	-3%	59.2	-16%	34.6	+3%	18.0	-7%	5	+2%
Germany	248.7	-9%	65.3	-10%	30.2	-9%	15.5	-6%	7.2	+4%
Luxemburg	240.6	-11%	73.7	-10%	23.1	-20%	18.9	+19%	8.2	-34%
United Kingdom	238.9	-9%	64.9	-17%	25.7	-11%	17.2	-1%	4	+11%
Austria	236.0	-8%	59.6	-10%	31.1	-12%	14.8	+14%	10.1	+3%
Portugal	224.7	-4%	46.6	-6%	28.6	+6%	16.4	+1%	7.5	+6%
Greece	218.4	-1%	77.1	-3%	15.8	+24%	4.6	+5%	16.6	-11%
Finland	212.3	-6%	54.8	-14%	19.1	-9%	8.6	+21%	7.7	+12%
Sweden	196.0	0%	33.6	-5%	21.3	+1%	7.9	0%	5.9	-3%
EU	254.3	-7%	70.9	-9%	26.8	-4%	16.3	-7%	10.8	-1%

[1] EU age-standardized rate per 100.000 population; [2] (1999 rate - 1994 rate) / (1994 rate); [3] Estimated death rate for 1999 and 1994-1999 variation unavailable

The unfavorable situation for men living in France is for the most part explained by the weight of UADT, liver and lung cancers. Thus, 65% of the total overmortality by cancer in France compared to the United Kingdom is due to a higher death rate for the three above localizations. For UADT cancers, France ranks first among EU countries with a major variation from all other countries. Regarding liver cancer, Italy, France and Greece take the lead with death rates of a similar order in all three countries. However, while mortality is decreasing markedly in Italy and Greece, French mortality rates are stagnating. With respect to lung cancer, Belgian and Dutch death rates are the highest but France ranks in the European average. However, although a drop in the number of lung cancers can be observed in many countries, French death rates are not falling significantly. In the case of mortality under 65, France is among the countries with the highest mortality for lung cancer along with Belgium and Spain.

Apart from the above specificities, France's situation is average or favorable for other types of cancers in men, while particularly high death rates are observed for certain localizations in other countries: stomach cancer in Portugal, prostate cancer in Sweden, colorectal cancer in Ireland and Denmark, skin melanoma in Denmark and Sweden.

In the under 65 population (Table 2.IV), France has the highest male mortality rate (together with Spain and Belgium). This is for the most part explained by the high frequency of lung cancers in all three countries. Similarly, France ranks at the top of all EU countries for "premature" mortality by UADT cancer (with Luxemburg) and by liver cancer (with Italy).

Table 2.IV: Standardized death rates by cancer in EU countries[1], male; under 65

	Total		Lung		Colorectal		UADT		Liver	
	1999	var/94[2]	1999	var/94	1999	var/94	1999	var/94	1999	var/94
France	119.6	-6%	38.6	-4%	7.7	-4%	17.3	-13%	6.5	-3%
Spain	107.8	-3%	38.6	+1%	8.6	+4%	11.0	-9%	4.9	+2%
Belgium[3]	99.3		40,4		8.0		10,5		2.2	
Portugal	93.0	-6%	23.6	-9%	9.9	+13%	11.5	+5%	2.9	-15%
Italy	91.9	-14%	29.8	-19%	7.6	-7%	6.3	-19%	6.8	-14%
Germany	91.2	-11%	27.2	-14%	9.4	-13%	10,6	-11%	2.8	+4%
Denmark[3]	90,2		26.2		9.8		8.3		1.6	
Austria	87.0	-9%	27.0	-9%	9.7	-14%	10,0	+12%	4.5	+13%
Netherlands	86.9	-9%	28.4	-17%	8.6	-2%	7.2	+14%	1.3	+44%
Luxemburg	86.5	-6%	31.1	-1%	7.0	+19%	16.3	+31%	2.8	-48%
Greece	86.3	0%	35.0	+1%	4.7	+15%	2.6	+30%	5.9	-3%
Ireland	84.6	-9%	17.8	-36%	12.7	+6%	8.7	+9%	1.8	+13%
United Kingdom	79.5	-7%	20,6	-15%	8.1	-12%	7.8	0%	1.6	+7%
Finland	68.4	-5%	17.9	-14%	6.2	+15%	4.6	+44%	2.6	+13%
Sweden	59.0	-10%	11.8	-17%	6.3	0%	3.8	+12%	2.2	+10%
EU	94.3	-8%	29.4	-11%	8.4	-6%	9.8	-8%	4.0	-5%

[1] EU age-standardized rate per 100 000 population; [2] (1999 rates – 1994 rates) / (1994 rates); [3] Estimated death rate for 1999 and 1994-1999 variation unavailable

Cancer mortality in women

Unlike men, French women occupy a generally favorable position within the EU (Table 2.V and 2.VI). For all localizations, female death rates by cancer are the highest in Denmark, Ireland, the United Kingdom and the Netherlands. The highest mortality rates are observed in Denmark and the Netherlands for breast cancer; in Denmark, the United Kingdom and Ireland for lung and UADT cancers; in Denmark and Germany for colorectal cancer; in Portugal for stomach cancer; and in Greece and Italy for liver cancer. In Denmark, lung cancer constitutes today the most frequent localization in women, ahead of breast cancer. In the United Kingdom, these two types of cancer exhibit the same frequency among the female population.

Table 2.V: Standardized death rates by cancer in EU countries[1]; female; all ages

	Total		Breast		Colorectal		Lung		Uterus[4]		UADT	
	1999	var/94[2]	1999	var/94	1999	var/94	1999	var/94	1999	var/94	1999	var/94
Denmark[3]	199.3		36.8		23.4		41.2				5.1	
Ireland	171.8	-6%	34.7	-8%	18.8	-9%	26.4	-8%	6.8	-6%	7.0	-17%
United Kingdom	167.3	-5%	31.8	-13%	16.4	-12%	30.7	0%	6.4	-12%	7.0	+3%
Netherlands	165.8	0%	36.6	-4%	19.0	-3%	23.1	+20%	6.1	-2%	5.0	+11%
Germany	151.0	-8%	28.5	-9%	20,4	-12%	15.3	+13%	7.3	-16%	3.3	+3%
Belgium[3]	147.7		33.6		17.9		16.4				3.5	
Austria	143.1	-10%	26.4	-15%	18.3	-8%	16.3	+7%	9.0	-14%	3.0	+43%
Sweden	141.8	+1%	22.4	-5%	14.7	-6%	18.5	+16%	7.2	+7%	2.4	-11%
Luxemburg	135.5	-10%	24.4	-27%	18.1	-20%	19.8	+24%	8.3	+28%	5.9	+79%
Italy	133.8	-8%	25.2	-12%	14.6	-9%	12.1	+3%	5.8	-21%	2.4	+4%
France	131.4	-1%	28.5	0%	15.2	-4%	11.3	+26%	7.0	-9%	3.5	+3%
Finland	125.1	-3%	23.9	+3%	12.1	-7%	10.7	+3%	5.3	-4%	3.1	-3%
Portugal	118.9	-5%	22.1	-11%	16.1	+5%	7.3	+3%	8.2	-14%	2.3	-21%
Spain	116.4	-5%	21.3	-13%	15.3	-3%	6.6	+14%	6.2	-13%	1.8	-10%
Greece	114.3	-1%	21.2	-9%	12.2	+22%	10,5	-2%	5.3	+13%	1.4	0%
EU	142.9	-5%	27.9	-9%	16.8	-8%	15.8	+5%	6.7	-13%	3.6	0%

[1] EU age-standardized rate per 100 000 population; [2] (1999 rates - 1994 rates) / (1994 rates); [3] Estimated death rate for 1999 and 1994-1999 variation unavailable; [4] Cervix and uterus

Table 2.VI: Standardized death rates by cancer in EU countries[1]; female; under 65

	Total		Breast		Colorectal		Lung		Uterus[4]		UADT	
	1999	var/94[2]	1999	var/94	1999	var/94	1999	var/94	1999	var/94	1999	var/94
Denmark [3]	95.8		22.6		7.8		23.1				2.7	
Netherlands	77.6	-3%	22.1	-6%	6.5	-6%	13.5	+11%	2.9	+7%	2.3	+10%
Ireland	76.2	-11%	22.8	-8%	6.3	-10%	9.2	-21%	4.4	0%	2.6	+8%
United Kingdom	73.9	-7%	19.2	-15%	5.4	-16%	11.8	-1%	3.6	-12%	2.5	+4%
Belgium[3]	68.3		21.1		5.6		9.2				2.1	
Germany	65.4	-9%	17.3	-10%	6.1	-12%	7.9	+14%	3.9	-15%	1.9	+6%
Austria	62.9	-11%	15.2	-16%	5.8	-8%	8.5	+8%	4.9	-13%	2.0	+54%
Sweden	62.9	-5%	13.4	-11%	4.5	-10%	10.1	+6%	3.7	+6%	0.8	-27%
France	61.6	+1%	18.0	+1%	4.9	-4%	6.6	+38%	3.5	-15%	2.1	+5%
Italy	58.4	-12%	15.3	-15%	5.4	-7%	5.3	0%	3.0	-19%	1.2	+9%
Portugal	56.5	-11%	14.3	-19%	5.9	+2%	3.7	+9%	4.8	-23%	0.9	-36%
Luxemburg	55.7	-18%	15.5	-16%	4.5	-13%	10.1	+2%	4.9	+20%	3.2	+167%
Spain	53.4	-9%	13.6	-20%	5.6	-2%	3.6	+24%	3.3	-18%	0.9	0%
Finland	52.5	-5%	14.9	-1%	4.1	+2%	4.2	0%	2.5	+25%	1.2	+33%
Greece	51.6	-5%	12.8	-16%	4.0	+18%	4.9	+7%	3.1	+15%	0.5	0%
EU	64.6	-6%	17.2	-10%	5.6	-7%	7.7	+10%	3.6	-12%	1.8	+13%

[1] EU age-standardized rate per 100 000 population; [2] (1999 rates - 1994 rates) / (1994 rates); [3] Estimated death rate for 1999 and 1994-1999 variation unavailable; [4] Cervix and Uterus

The evolution of female death rates by cancer between 1994 and 1999 shows a downward trend (with the greatest decrease in Austria and Luxemburg). Compared with this general trend, however, stagnation in the mortality levels is seen for certain countries, including France. The stability of death rates in France is for the most part explained by the observed trends with lung, UADT, breast and uterine cancers. Women living in France currently exhibit the highest increase in lung cancers (along with Luxemburg and the Netherlands) and this unfavorable position is even more marked for deaths under 65 (40% death rate progression between 1994 and 1999). For UADT cancers, Luxemburg and Austria exhibit the most marked rise in death rates (female rates are also rising in France but not as markedly as in these two countries). While death rates by breast and uterine cancers are falling in most EU countries, they are stagnant in France.

Variation between male and female death rates

Male overmortality by cancer is observed in all countries (Table 2.VII) but the largest variation between the sexes is seen in Spain and France where the death rate is 2.2 times higher in men. Conversely, the differences between the sexes are the lowest in Denmark, Sweden and the United Kingdom (1.3). In terms of localization, male overmortality is the highest for UADT and lung cancers (4.5 for the whole of the EU). Male mortality rates by lung cancer are 12 and 7 times higher than the rates for women in Spain and France respectively. Similarly, the figure for male overmortality by UADT cancer is about 10 in both countries. Conversely, the mortality ratios between sexes for these localizations are particularly low in Denmark, Sweden and the United Kingdom (about 2). Between 1994 and 1999, the level of male overmortality has remained stable, except in the case of lung and UADT cancers where the difference between men and women has been reduced.

Table 2.VII: Men/women ratios of death rates by cancer in EU countries[1]; all ages; 1999

	Total	UADT	Lung	Liver	Kidney-bladder	Stomach	Colorectal	Hemolym-phatic tissues
Spain	2.3	9.1	12.0	2.7	5.1	2.3	1.8	1.6
France	2.2	7.5	6.6	4.9	3.6	2.6	1.8	1.6
Italy	1.9	4.8	6.5	2.7	4.6	2.2	1.7	1.6
Belgium[3]	1.9	4.8	6.3	2.1	3.1	2.2	1.5	1.7
Greece	1.9	3.3	7.3	2.3	4.3	2.3	1.3	1.6
Portugal	1.9	7.1	6.4	2.9	3.4	2.1	1.8	1.3
Luxemburg	1.8	3.2	3.7	4.1	2.7	2.1	1.3	2.0
Finland	1.7	2.8	5.1	1.9	2.9	2.1	1.6	1.5
Netherlands	1.7	3.0	3.7	2.2	2.8	2.4	1.5	1.5
Austria	1.6	4.9	3.7	3.0	2.6	1.8	1.7	1.5
Germany	1.6	4.7	4.3	2.5	2.9	1.9	1.5	1.5
Ireland	1.5	2.6	2.2	2.1	2.7	1.9	1.8	1.6
United Kingdom	1.4	2.5	2.1	2.0	2.7	2.5	1.6	1.5
Sweden	1.4	3.3	1.8	1.8	2.2	2.0	1.4	1.5
Denmark[3]	1.3	3.1	1.7	1.5	2.6	2.3	1.4	1.7
EU	1.8	4.5	4.5	2.8	3.2	2.1	1.6	1.5

[1] Standardized men/women death rate ratios; [2] including lymphomas; [3] Estimated ratios

Comparability of data from one country to another

It is necessary to investigate whether the comparisons between countries on which the preceding results are based are legitimate. The degree of comparability of data on causes of death in the EU is currently being analyzed as part of Eurostat's "Causes of death " Task Force (specific certification and codification practices by country). In this respect, a report is available that contains recommendations validated by all EU countries for improving the quality and comparability of data as well as a bibliography of the main scientific studies published on the subject (Jougla et al., 2001).

Although methods to obtain data on causes of death are being increasingly standardized over time, numerous analyses have highlighted the disparity between different countries' practices, whether in terms of medical certification of the causes of death or codification (selection of an initial cause for each death). Regarding medical certification, it is worth noting that all EU countries now use a death certificate similar to the one recommended by WHO in the International Classification of Diseases (ICD), which involves a common methodology to describe the morbidity process that lead to death (from an initial to an immediate cause). Similarly, EU countries apply ICD rules with increasing homogeneity in order to select the initial cause (on which death statistics are based) from the list of possible causes on the death certificate (WHO, 1992). The current trend toward automatic codification systems integrating identical decision rulings for choosing the initial cause of death will strongly contribute to achieve good standardization of the codification step.

Among different causes of death, cancer is one of the causes for which the degree of international comparability is most reliable (compared to pathologies such as cardiovascular diseases or violent deaths), especially when using fairly broad localization subgroups (Jougla et al., 2003). Nevertheless, certain localizations are a greater source of recording problems than others. Lung cancer, the most frequent tumor site for men, is characterized by a satisfactory concordance between information that comes from mortality and morbidity. In the case of breast cancer, studies based on a comparison of the "official" initial cause of death and the cause determined from other clinical sources conclude there is a slight underestimation in official statistics. For other anatomical sites, differences in recording practices may lead to comparability bias. These differences may be due to a difficulty in confirming the malignant or primitive character of a tumor (liver), or distinguish the primary site among neighbor organs (stomach-esophagus, pancreas-biliary tract, cervix-uterus), especially when clinical manifestations or histological typing are similar. Finally, the role of certain cancers with rather favorable prognosis in the death process can be overestimated compared to heavy associated pathologies (prostate and colon). Aside from potential bias linked to diagnostic difficulties or lack of precision in the declaration on the part of certifying practitioners, the data can be affected by random fluctuations, especially when death rates analyzed for a given country are low (skin melanomas, "premature" cancers of the urinary tract, etc.).

In conclusion, the results of analyses of mortality levels by cancer show major spatial disparities between EU countries. Thus, France's situation with respect to male cancer levels is not favorable. This unfortunate position is largely explained by very elevated death rates for lung, UADT and liver cancers. While occupational exposure certainly carries a good deal of weight as a determinant of mortality levels (though this is not easily measured for lack of available data), we know that these types of cancers are strongly linked to two risk factors: alcohol abuse and smoking. Similarly, though France appears to be in a rather favorable position for female cancers, a very worrying trend is observed with respect to lung cancer. Given the delayed impact of tobacco consumption, the evolution of mortality is the

consequence of the surge in women's smoking habits since the 60's. The situation is all the more worrying that current indicators of female tobacco consumption are not encouraging (Beck and Legleye, 2003). Analysis of disparities by cancer category in the EU clearly shows the particularly negative and strong impact of alcohol and tobacco consumption on mortality levels in France compared to other countries. The repercussions of tobacco and alcohol consumption can also be observed in other countries, particularly in the case of women. With respect to breast and uterine cancers, no change has been recorded in France while many other countries exhibit a decrease in such cancers. In this respect, one might question the impact of national screening policies (Uhry et al., 2003) but the results must be confronted with incidence and survival data. This study also showed higher mortality rates for specific localizations (stomach, prostate, colon-rectum, skin melanomas) in other countries. Eurostat has established an Atlas that maps such causes of deaths down to the regional level and thus allows a more precise characterization of spatial mortality disparities across the EU (Jougla et al., 2003).

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3

Incidence and evolution of child cancers in France

In France as in all industrialized countries, 1 child in 500 is affected by cancer before the age of 15. The last census estimated the number of children under 15 living in France (excluding overseas territories) at 10.5 million. Among them, almost 1.500 new cancer cases are detected every year. Over half of these cancers occur before the age of 6. Leukemia is the most common form of cancer in children, with 450 new cases every year. Contrary to findings in adults, chronic lymphoid leukemia is not found in children; there are less than 10 cases of chronic myeloid leukemia each year and acute leukemias that develop from lymphocyte precursors are predominant. Brain tumors rank second in terms of frequency, with about 300 new cases every year. One in two cases is an astrocytoma, and one in four cases is a primitive neuro-ectodermic tumor. This distribution is again very different from the distribution in adults where high-grade gliomas and meningiomas are predominant. Child brain tumors are more often differentiated and infratentorial. Meningiomas and especially acoustic neurinomas or epiphyseal adenomas are rare. Finally, embryonic tumors are predominant among other types of tumors. Carcinoid tumors are extremely rare, particularly before the age of 5.

Incidence of child cancers in France

Child cancer recording in France (excluding overseas territories) was accomplished in two major steps. Between 1983 and 1990, pediatric cancer registers were set up on a regional basis, first in Lorraine (1983), then in the PACA (Provence, Alpes, Côte d'Azur) region (1984), in Auvergne (1986), in the Rhône-Alpes region (1987), in Brittany (1991), and in the Limousin (1994). A register was also set up in the Val de Marne between 1990 and 2000. Incidence data from these registers over the period 1990-1999 is summarized in Table 3.I and has been published recently (Desandes et al., 1994).

Table 3.I: Incidence of child cancer in France, pediatric register data over the period 1990-1999 (from Desandes et al., 2004)

Type of tumor	% of total	< 1 year	1-4 years	5-9 years	10-14 years	ASR*	M/F
Leukemias	**30.2**	**42.2**	**68.7**	**34.3**	**23.2**	**42.3**	**1.1**
Acute lymphoid	23.5	16.7	59.2	26.5	17.1	33.1	1.2
Acute non-lymphoid	5.4	20.6	8.1	6.6	4.3	7.5	0.8
Chronic myeloid	0.7	2.5	0.7	0.6	1.2	0.9	1.1
Others	0.3	1.5	0.4	0.3	0.2	0.4	0.6
Non specified	0.3	1.0	0.4	0.4	0.5	0.4	1.0
Lymphomas	**12.4**	**3.9**	**9.3**	**20.0**	**20.6**	**15.6**	**2.2**
Hodgkin's disease	4.4	0.0	1.6	5.5	10.5	5.3	1.8
Non-Hodgkin's non-Burkitt's lymphomas	3.7	0.5	3.4	6.2	5.4	4.7	2.0
Burkitt's lymphomas	3.6	0.0	3.3	7.6	3.9	4.6	3.3
Others	0.4	3.4	0.7	0.4	0.2	0.7	1.7
Non specified	0.3	0.0	0.4	0.3	0.6	0.4	1.2
CNS tumors	**21.8**	**34.3**	**30.6**	**29.2**	**26.1**	**29.1**	**1.1**
Ependymomas	3.0	12.3	6.6	2.0	2.3	4.3	0.8
Astrocytomas	9.1	7.8	12.2	11.8	12.8	11.9	1.1
Primitive neuroectodermic tumors	4.2	6.9	5.4	7.2	3.7	5.6	1.8
Other gliomas	2.6	2.9	2.9	3.9	3.4	3.4	1.0
Others	2.4	2.9	3.0	3.4	3.2	3.2	1.1
Non specified	0.5	1.5	0.5	0.7	0.7	0.7	0.4
SNS tumors	**9.1**	**69.6**	**24.5**	**2.4**	**1.3**	**14.1**	**1.2**
Neuroblastomas and ganglioneuroblastomas	8.9	69.6	24.1	2.3	0.9	13.9	1.2
Others	0.2	0.0	0.4	0.1	0.4	0.2	1.7
Retinoblastomas	**2.3**	**20.6**	**6.0**	**0.5**	**0.2**	**3.7**	**1.3**
Renal tumors	**6.0**	**20.1**	**18.2**	**4.7**	**1.3**	**9.1**	**0.7**
Nephroblastomas, rhabdoid and clear cell sarcomas	5.9	20.1	18.1	4.6	0.7	8.8	0.6
Renal carcinoma	0.2	0.0	0.1	0.1	0.6	0.2	1.7
Non specified	0.0	0.0	0.0	0.0	0.0	0.0	-
Hepatic tumors	**1.0**	**5.4**	**2.8**	**0.3**	**0.5**	**1.5**	**2.2**
Hepatoblastomas	0.8	5.4	2.7	0.2	0.0	1.3	2.2
Hepatic carcinomas	0.2	0.0	0.1	0.1	0.5	0.2	2.5
Non specified	0.0	0.0	0.0	0.0	0.0	0.0	-
Bone tumors	**5.5**	**0.5**	**2.5**	**5.3**	**14.1**	**6.6**	**1.3**
Osteosarcomas	2.7	0.0	0.4	1.6	8.6	3.1	1.7
Chondrosarcomas	0.1	0.0	0.0	0.1	0.3	0.1	1.0
Ewing's sarcoma	2.4	0.5	1.9	3.4	4.6	3.0	0.9
Others	0.2	0.0	0.1	0.2	0.4	0.2	1.3
Non specified	0.1	0.0	0.1	0.1	0.3	0.1	1.5
Soft tissue sarcomas	**5.4**	**14.2**	**7.7**	**6.2**	**6.4**	**7.4**	**1.6**
Rhabdomyosarcomas and embryonic sarcomas	3.1	5.9	5.7	4.1	2.5	4.3	1.7
Fibrosarcomas, neurofibrosarcomas	0.5	2.9	0.2	0.2	1.0	0.7	1.1
Kaposi's sarcoma	0.0	0.0	0.0	0.1	0.0	0.0	0.0
Others	1.3	5.4	1.2	1.1	1.8	1.7	1.8
Non specified	0.6	0.0	0.6	0.7	1.1	0.7	1.8
Germinal and gonadal cell tumors	**3.4**	**11.8**	**4.3**	**1.7**	**5.9**	**4.5**	**0.9**
Germinal intracranial or intraspinal	1.2	1.5	1.0	1.0	2.7	1.5	1.7
Other germinal or non specified	0.7	6.4	1.8	0.1	0.0	1.1	0.6
Gonadal germinal	1.2	2.5	1.4	0.5	2.5	1.5	0.8
Gonadal carcinomas	0.1	0.0	0.0	0.1	0.4	0.1	0.0
Other gonadal or non specified	0.2	1.5	0.1	0.0	0.4	0.3	0.6
Carcinomas and other epithelial tumors	**2.7**	**0.0**	**1.0**	**3.3**	**6.7**	**3.3**	**1.0**

Corticosurrenal carcinoma	0,1	0,0	0,5	0,1	0,1	0,2	2.0
Thyroid carcinomas	0,9	0,0	0,2	1.2	2.3	1.1	0,8
Nasopharyngial carcinomas	0,3	0,0	0,0	0,1	1.0	0,3	3.0
Malign melanomas	0,3	0,0	0,0	0,5	0,7	0,4	0,4
Skin carcinomas other than melanoma	0,3	0,0	0,0	0,7	0,4	0,3	1.2
Others or non specified	0,8	0,0	0,2	0,7	2.2	1.0	1.1
Other tumors and non specified tumors	**0,2**	**0,5**	**0,1**	**0,2**	**0,3**	**0,2**	**1.3**
Other malignant tumors	0,1	0,5	0,1	0,1	0,2	0,2	1.5
Non specified malignant tumors	0,0	0,0	0,0	0,1	0,1	0,1	1.0
All tumors	100,0	223.1	175.8	108.0	106.5	137.5	1.2

* World age-standardized rate per 1 000 000 children per year

A second step lead to national recording of child cancers (as of 1990 for malignant hemopathies and since 2000 for other tumors) while keeping regional registers active since they are more suited for work on follow-up and management of child cancers. The National Register for Child Cancers (*Registre National des Leucémies de l'Enfant* - RNLE) is directed by Jacqueline Clavel from Inserm Unit 170 in Villejuif. The National Child Solid Tumors Register (*Registre National des Tumors Solides de l'Enfant* - RNTSE) in Nancy is directed by Brigitte Lacour, who is also in charge of the Lorraine child cancer register. The recently published incidence data from RNLE (Clavel et al., 2004) are of course more precise with respect to malignant hemopathies than the regional data but estimates are analogous to those made by regional registers. Apart from estimating cancer incidence and working on surveillance, the two registers also carry out etiological research as part of the Inserm Unit 170 research project on environmental and genetic risk factors for child cancer[5].

Geographical variations of incidence

When focusing on histological typing, a particular localization or age group, numbers become restricted and incidence estimates fluctuate, particularly when they are based on data from regional or departmental registers. This can make geographical and temporal comparisons difficult. Nonetheless, a number of facts have been well established:

- Burkitt's lymphomas are more frequent in countries with endemic malaria;
- Leukemia incidence is higher in industrialized than developing countries.

The incidence of leukemia is also higher in Hong-Kong than other Asian countries, in white compared to black people in the United States, and in non-Maoris compared to Maoris in New-Zealand (Parkin et al., 1998). Socio-economic conditions and hygiene, nutritional factors, tobacco consumption and accompanying environmental exposure certainly play a major role in accounting for this imbalance. Making abstraction of such intra-country variations however, the figures for Western countries are on the whole quite homogeneous. Within European countries (Automated Childhood Cancer Information System or ACCIS), fluctuations can be quite pronounced (Table 3.II) but no spatial organization or gradient can be identified by making international comparisons.

[5] This program comprises national case-control studies, family studies, ecological studies on the risk associated with ionizing radiations and certain population characteristics, and the setting up of studies coupled with geographical information systems on various sources of environmental exposure.

Table 3.II: Age-standardized incidence rates (ASR) of cancers in children under 15 in Europe (ACCIS, 2003)

	Europe	Northern Europe	United Kingdom	Central Europe	Eastern Europe	Southern Europe	France
Leukemias	44.1	48.5	43.6	45.1	39.2	43.3	42.3
Lymphomas	15.0	15.8	11.7	13.8	17.6	19.8	15.6
CNS Tumors	27.6	44.1	30.8	23.0	27.3	29.9	29.1
SNS Tumors	10,4	8.9	9.5	11.0	9.3	11.3	14.1
Retinoblastomas	3.6	5.0	4.6	3.0	3.3	3.6	3.7
Renal tumors	8.4	9.1	7.9	8.3	8.5	8.6	9.1
Hepatic tumors	1.4	2.2	1.2	1.2	1.7	1.4	1.5
Bone tumors	5.3	5.2	4.8	5.0	5.3	6.9	6.6
Soft tissue sarcomas	8.5	10.9	9.9	7.6	7.7	9.7	7.4
Germinal cell tumors	4.2	4.9	3.9	4.3	3.6	4.1	4.5
Carcinomas	4.0	4.4	3.5	2.0	9.7	4.1	3.3
Other or non-specified tumors	1.1	3.2	1.1	0,3	1.8	1.6	0.2
All tumors	133.5	162.2	132.5	124.6	134.8	144.2	137.5

Northern Europe (Denmark, Finland, Island, Ireland, Norway, Sweden), Eastern Europe (Belarus, Bulgaria, Estonia, Hungary, Latonia, Lithuania, Poland, Rumania, Slovakia), Central Europe (Austria, Belgium, France, Germany, the Netherlands, Switzerland), Southern Europe (Croatia, Italy, Malta, Portugal, Slovenia, Spain, Turkey, Yugoslavia).

Temporal variation in child cancer incidence

The trend toward an increase in cancer incidence is far from being claimed unanimously. In France (Figures 3.1 and 3.2), the trend over the period 1990-1999 is not one of increase. The data from the Lorraine child cancer register (*Registre Lorrain des Cancers de l'Enfant*), which started keeping records in 1983, does not show evidence of an incidence increase either.

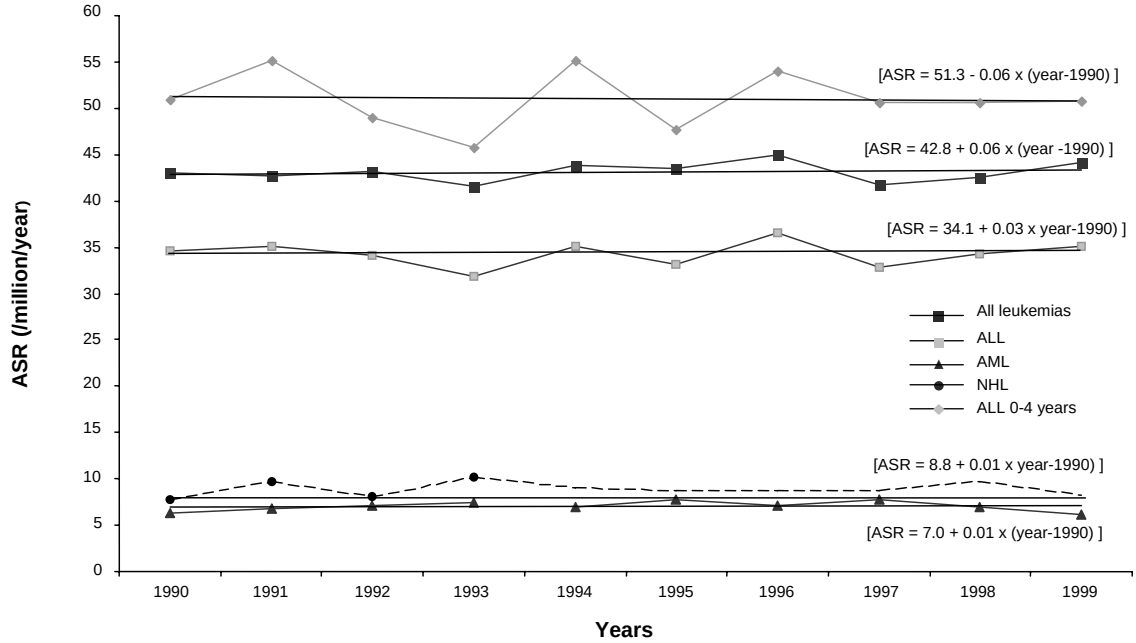

Figure 3.1: Evolution in the incidence of child malignant hemopathies in France over the period 1990-1999 - *Registre National des Leucémies et des Lymphomes de l'Enfant* (from Clavel et al., 2004)

ALL: Acute Lymphocytic Leukemia; AML: Acute Myeloid Leukemia; NHL: Non-Hodgkin's Lymphoma

International data that goes further back in time shows a coherent increase in solid tumors from one country to the next during the 1980's. It is now well established that the break in the incidence curve was due to the brain imagery revolution (Smith et al., 1998). For other tumors, the data is contradictory and it is hard to separate improved diagnosis from better codification (to ensure quality recording) to explain the increase in the number of cases. In Western countries, no spatial organization has been identified that can distinguish countries with an incidence increase from those where incidence has remained stable. The recently published analysis of European data by ACCIS *(*Automated Childhood Cancer Information*)* (Steliarova-Foucher et al., 2004) shows an increase in the incidence of child cancers (0-19 years) from 1970 to 1990 in all age groups studied. The mean annual variation was 1% during the 1970's and 1980's, and 1.3% during the 1980's and 1990's. The increase is more significant in Eastern compared to Western European countries. However, the heterogeneity of registers included in this analysis urges one to interpret such results with caution.

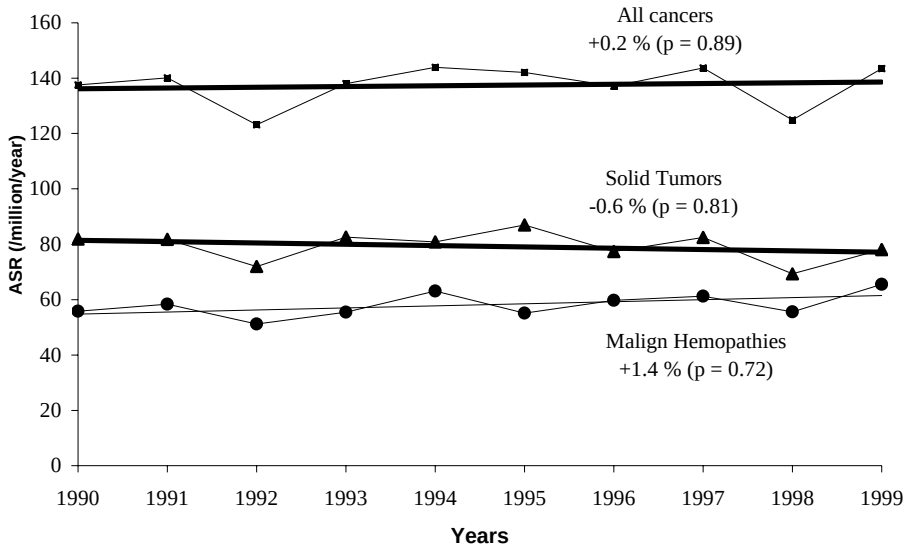

Figure 3.2: Evolution in the incidence of child cancers in France over the period 1990-1999 – ***Registres régionaux de cancers de l'Enfant*** **(from Desandes et al., 2004)**

Geographical and temporal incidence variations on a small geographical scale

Over the last twenty years, cancers, and in particular child leukemia, have been studied on a small temporal and geographical scale, when case occurrence can be considered over short distances. The aim of such studies is to show possible trends of spatio-temporal case clusters suggesting the presence of carcinogenic sources or localized epidemics. This issue remains hotly debated and has lead to the development of important new methodological techniques.

In conclusion, the increased incidence in child cancers often reported in the media is based on inconsistent reports and cannot be accepted as an established fact. Conversely, the possible link between environmental exposure and the occurrence of several types of child cancers, particularly malignant hemopathies and brain tumors, is increasingly well documented. However, a clear causal relationship has only been shown in the case of

exposure to high doses of ionizing radiation. The role of infectious agents in Burkitt's lymphoma and Hodgkin's disease (EBV) has also been clearly demonstrated and is strongly suggested in acute leukemias and, to a lesser degree, in brain tumors. Arguments are slowly accumulating to suggest that low doses of radiation (particularly of natural origin), very low frequency magnetic fields, pesticides and atmospheric pollution generated by automobile traffic may also play a role. Whether it is responsible or not for a detectable increase in cancer incidence, the environment is probably involved in the occurrence of a number of child cancers.

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II

Elements of methodology

Introduction

Identification of carcinogens in the environment is usually based on the demonstration of a causal relationship between exposure to a given agent and cancer in humans. On the basis of epidemiological studies that show such a relationship, estimates of attributable risks for different carcinogens can then influence decisions on priority measures to be taken for cancer prevention.

Experimental approaches to identify carcinogens played a crucial role until the 1960's, after which the idea that epidemiological results were sufficient in themselves to prove a causal relationship was accepted. Later, epidemiological results were considered to be the only acceptable proof of causal relationship. However, the lag time before exposure and the occurrence of disease can be long, thereby delaying primary prevention while waiting for epidemiological results. Experimental results, particularly long-term carcinogen tests, can help offset this problem. In some cases, they represent valid predictors of cancer risk in humans. Testing chemicals for carcinogenicity before they are produced on an industrial scale and allowed to spread in the environment certainly has contributed to primary prevention of human cancers though it is difficult to measure the extent of this contribution. The experimental and epidemiological approaches are therefore complementary in their role to identify carcinogens.

Up until 2002, the International Agency for Research on Cancer (IARC) had identified 87 carcinogenic agents or forms of exposure on the basis of epidemiological results (industrial processes, chemicals or chemical mixtures in the workplace, drugs, lifestyle habits, biological agents). Based on a combination of epidemiological and experimental data, another 63 chemicals or chemical mixtures were proposed as probable and 234 products as possible human carcinogens.

Primary cancer prevention must associate a reduction in the number of carcinogens to which man is being exposed and a reduction in exposure levels. The latter is essential even for low-dose exposure. When large population groups are exposed to relatively low levels of carcinogens, reduction of exposure will have a numerically significant impact in terms of prevention. Furthermore, low-level carcinogen exposure can turn out to be dangerous if there is concomitant exposure to other agents and a synergistic interaction is present. Dose-response relationships and the definition of thresholds can therefore have important consequences on primary prevention.

Multiple factors are likely to be involved in the occurrence of cancer. Quantitative estimates of attributable risks to various etiological factors remains very imprecise: nutrition, occupational exposure, pollution, etc. Some believe the majority of cancers originate from certain types of behavior and life style. This view minimizes the role played by environmental agents whether or not they are occupational exposure factors for which a causal relationship has already been demonstrated. It is generally recognized that 50% of cancers could be avoided if existing etiological knowledge was applied. Attributable risk depends in particular on the strength of the relationship between the exposure factor and cancer, and on the prevalence of this factor in the population.

Individual genetic susceptibility can also modulate environmental effects. It is now well known that gene polymorphism can play a role in the activation or detoxification of certain carcinogens. Similarly, polymorphism of genes involved in DNA repair, receptors, oncogene

homologues or tumor suppressors can also affect susceptibility to environmental exposure and account for risk through a wide variety of processes. The more we know about susceptibility genes, the easier it will be to identify potentially fragile sub-populations.

Thus, the relationship between the environment and cancer has been examined using a variety of approaches. These studies bring arguments and proofs that complement each other and concur to develop a validated body of knowledge that might eventually lead to the drafting of practical guidelines and recommendations.

4

Causality criteria

Causality is a complex concept and requires that a causality model be defined before it can be analyzed. In the case of biological phenomena, such a model is generally multifactorial since it involves several causes that form a sufficient set of contributive causes for an event to occur (for instance, the appearance of a disease in a particular subject). Such contributive causes must be encountered either jointly or sequentially. There may be several sets of coexisting sufficient contributive causes for a single event.

Unlike causality relative to certain physical phenomena, causality in biology involves stochastic elements that allow modeling of unknown factors involved in the causal relationship. For example, in the case of a smoker whose tobacco consumption is precisely known over a time course, it is not possible to determine with certainty whether the subject is going to develop lung cancer but epidemiological data can provide a risk estimate, i.e. the probability that the subject will developing lung cancer in the course of time. By taking into account other factors known to influence such a risk (occupational exposure to asbestos, for example) or yet unknown risk factors and their interaction, one can theoretically refine the risk estimate. Thus the stochastic element is reduced with the advancement of knowledge. According to certain authors, stochastic elements governing the occurrence of an event remain even when all the contributive causes of a sufficient causal set are gathered, above and beyond the stochastic modeling of fundamentally determinist phenomena (once all causal elements are known). A thorough discussion of the above concepts can be found in reference works on epidemiology (Kleinbaum et al., 1982; Rothman and Greenland, 1998).

Epidemiological studies allow the identification of relationships between exposure factors and the risk of disease occurrence. Measures of association such as the relative risk or the odds ratio are calculated on the basis of such studies in order to quantify the strength of such relationships. In the case of a positive relationship, i.e. if the risk of disease increases with the degree of exposure to the factor under consideration, and after having allowed in as much as possible for the various biases possible in epidemiological studies, the factor can be considered to be a risk factor. However, this does not provide absolute proof that there exists a causal relationship between the risk factor and the occurence of the disease. Now, can one indeed obtain proof of the causal nature of such a relationship? According to Hume (1739) with whom Popper (1959) agrees, while a hypothesis (relative to a causal relationship, for instance) can very well be refuted by experimentation or observation that is incompatible with the hypothesis, proof of a hypothesis is on the contrary impossible to obtain. One can at best verify repeatedly and under varying circumstances the consistency of results with such a hypothesis.

Hill's Criteria

In spite of these theoretical restrictions, epidemiologists endeavor to judge the degree of causality plausibility of a relationship on the basis of available data, both in order to improve knowledge about disease determinants and to propose preventive measures. This approach is complicated by the fact that epidemiological studies are more often than not observational (cohort and case-control studies, for example) rather than experimental. In this respect, it must be pointed out along with Rothman and Greenland (1998) that results from experimental studies (randomized trials, for instance) can show discrepancies between studies or be interpreted in diverging ways and that conversely, the non-experimental nature of a discipline does not necessarily impede major scientific progress (e.g. understanding the movement of planets, plate tectonics or the evolution of species).

In practice, the chosen approach is based on a set of criteria to be confronted in order to judge the degree of causality plausibility of a relationship. Such criteria are examined one by one and then analyzed synthetically in order to progress and generally assess plausibility. It is worth mentioning that such an overall judgment does not entail assigning a score value or obtaining a numerical result even if categories of causality plausibility level are used by certain organizations (see below).

The most commonly used criteria are those proposed by Hill (1965). These criteria include and add to the criteria proposed in 1964 in the American Surgeon General's report about the effects of smoking on health (United States Department of Health, Education and Welfare, 1964) and are akin to the rules proposed earlier by Hume (1739) and to Mill's inductive canons (1862). There are nine such criteria (Table 4.I), the first five of which characterize the nature of the relationship between the exposure factor under consideration and disease risk as a function of the results obtained from epidemiological studies. The last four criteria serve to put the results of the epidemiological studies into perspective relative to biological knowledge pertaining to the relationship under study. It is worth noting that some versions of this set of criteria only take into account seven criteria by doing away with the last two of the second group criteria, or even six criteria by fusing the first two criteria from the second group.

Table 4.I: Hill's causality criteria (1965)

Strong relationship
Dose-effect relationship
The cause precedes the effect
The relationship is specific
Results are reproducible
Biological plausibility
Biological coherence
Experimental data available
Analogy

Criteria that characterize the nature of the relationship

Among the five criteria that characterize the nature of the relationship, the first four are involved with the results of individual epidemiological studies. They can therefore be verified by some studies and not others. They may also be involved in synthesis of

epidemiological studies in the form of meta-analyses. The fifth criterion (reproducibility) concerns the confrontation of results from various epidemiological studies.

Strength of relationship

The strength of the association is quantified, for instance, by measures of association such as the relative risk and odds ratio. The higher these estimated values in the epidemiological studies, the greater the strength of association. Given that epidemiological studies are for the most part observational in nature, biases may cause result distortion and thus lead to fortuitous associations. In this respect, a quantitatively strong association is less likely to be explained by bias than a weak association. In particular, in order for a third known or unknown factor to explain such an association (confounding bias), it would need to display a stronger association with the disease risk than the exposure factor under consideration. Generally speaking, only one or more strong biases could possibly account for a strong association. A strong association therefore makes causality more probable (or less improbable). Conversely, even a weak bias might account for a weak association.

For these reasons, the strength of the association is generally considered, as one might guess intuitively, to be a strong causality criterion. However, it is not a necessary criterion for causality. For example, in spite of its weak quantitative association, passive smoking is now considered to be a cause of lung cancer (International Agency for Research on Cancer Working Group for the Evaluation of Carcinogenic Risks to Humans, 2004). It is, however, not a sufficient causality criterion since, even in the case of a strong association, one cannot eliminate the possibility that a confounding factor that is more strongly associated with the risk of disease occurrence, but is unknown or has not been taken into account, is actually responsible for this association.

Dose-effect relationship

This criterion, also called "biological gradient", refers to the presence of a monotonic relationship between the level of exposure to the factor under consideration (or "dose") and the risk of developing the disease under scrutiny (or "effect"). The term "monotonic trend" is sometimes used to describe such a relationship. This criterion is generally considered to be a strong causality criterion in as much as one expects increasing exposure to lead to more serious tissue lesions and hence facilitate the pathological process. Nonetheless, it is not a necessary causality criterion since other forms of dose-effect relationship can exist, such as the threshold relationship observed for the association between diethylstilbestrol (DES) and vaginal adenocarcinoma. Neither is it a sufficient causality criterion since, even in the presence of a clearly apparent monotonic dose-effect relationship, one cannot eliminate the possibility that a known or unknown confounding factor – itself presenting a strong monotonic association with the risk of disease occurrence but not taken into account in the available studies – is responsible for this apparent dose-effect relationship. One can nevertheless assert that the absence of a monotonic dose-effect relationship allows refutation of causal hypotheses involving a monotonic dose-effect relationship.

Temporality

This criterion merely refers to the fact that the cause, i.e. exposure, must precede the effect, i.e. the occurrence of disease. Establishing this temporal relationship is essential to consider the possibility of a causal relationship and this criterion is therefore a necessary causality criterion. Nonetheless, it is clearly not a sufficient criterion. Furthermore, observing persisting exposure in some cases after occurrence of the disease is not incompatible with causality. However, if exposure is only observed after occurrence of the disease, this means

exposure was not responsible for the disease. In conclusion, though relationship temporality is a necessary criterion, it is difficult to characterize it as a strong or weak causality criterion.

Specificity

This criterion means that a single cause must lead to a single effect, i.e. that only one disease caused by a particular exposure can be associated with the causal exposure. The justification of its inclusion as a causality criterion is that it suggests the existence of a specific mechanism for the disease under scrutiny, which infers the existence of a causal relationship. Nonetheless, this criterion is highly questionable and does not seem to be an appropriate causality criterion even if it is often treated as such. Indeed, there is no strong justification for this criterion since the fact that exposure might be causal for diseases other than the one that is being studied neither reinforces nor diminishes the probability that such exposure is also causal for the disease under scrutiny. Furthermore, Hill himself (1965) had many reservations as to the use of this criterion. In practice, there are numerous examples of exposure that is causal for several diseases, smoking being an obvious one. In conclusion, it is a weak and perhaps altogether invalid criterion that is of course neither necessary nor sufficient for establishing a causality relationship.

Reproducibility of relationship

This criterion refers to reproducibility of observation between studies that an association exists between an exposure factor and a disease. This criterion is strenghthened when the studies are carried out in different contexts and with differing populations. It is generally considered to be a strong causality criterion. However, it is not a necessary criterion. Indeed, differing results between studies can come from differences in methodology or from random variability between studies. More importantly, if the factor under consideration is causal but other contributive causes intervene to constitute a sufficient causal set (see above), the differences between studies may come from differences in the prevalence of such contributive causes for different populations or time periods from one study to another, as discussed by Rothman and Greenland (1998). Neither is this criterion sufficient of course if only because the same confounding bias and other biases can be found in the various studies under consideration. According to Rothman and Greenland (1998), the only real point in paying attention to consistency between results from different studies is to be able to eliminate the hypothesis that a third factor exhibiting a strong variation from one study to the next might be responsible for important differences between the studies.

Contextual criteria

The last four criteria involve biological knowledge about the association under scrutiny.

Biological plausibility

This criterion determines whether the association considered is coherent in terms of general biological knowledge. It is usually considered to be a strong causality criterion since a causal association must necessarily be based on biological mechanisms. However, it is not a necessary causality criterion since the absence of relevant biological knowledge on a given subject may be temporary and merely reflect the current state of scientific knowledge. To illustrate this, Rothman and Greenland (1998) point out that the scientists who made the first hypotheses about typhus transmission in the 19th century were criticized for the lack of plausibility of their hypotheses because biological knowledge on transmissible diseases was limited at the time. Conversely, biological plausibility is not a sufficient causality criterion since biological mechanisms elucidated on the basis of *in vitro* or animal studies are not necessarily transposable to man *in vivo*.

Biological coherence

This criterion is verified when the causal interpretation of the association under consideration is not in contradiction with available knowledge on the natural history and biology of the disease studied. It is very similar to the previous criterion and a clear distinction is not always made between the two. Nevertheless, the present criterion has to do with confronting the causal interpretation of the association with effectively available knowledge about the disease rather than general biological knowledge, which is the case for the previous criterion. In this respect, biological coherence is sometimes seen as a necessary causality criterion in that the existence of a contradiction between the proposed causal interpretation and the available biological knowledge on the subject may lead to a rejection of the causal interpretation. Nonetheless, it is sometimes tricky to judge accurately whether such a contradiction exists and this judgment can evolve according to available knowledge.

Presence of experimental data

This criterion appears to be ill-defined by Hill (1965). It may encompass both the presence of experimental biological or animal data as well as data on the effects of eliminating a harmful exposure situation from a population. The existence of *bona fide* experimental data on the effects of exposure in man is rare. Such data exists sometimes in intervention trials aimed at verifying certain hypotheses such as the relevance of a given prevention policy (for example, vitamin supplement supplementation). In any case, this criterion is neither necessary nor sufficient to confirm causality. Given the uncertainties involved in the definition of this criterion, it is difficult to judge whether it is a strong or a weak causality criterion. Indeed it is sometimes omitted from the list of causality criteria (Kleinbaum et al., 1982).

Analogy

This involves analogy with other causal relationships and their mechanisms. This criterion is neither necessary nor sufficient. It is considered to be a weak criterion because of its strong subjectivity and is sometimes also omitted from the list of causality criteria, like the previous criterion (Kleinbaum et al., 1982).

In conclusion, the use of Hill's criteria to determine the causal nature of an association is rather delicate. Only five of the seven criteria are generally considered to be strong criteria: strength of association, the existence of a monotonic dose-effect relationship, reproducibility of the association, biological plausibility and biological coherence, which are not always properly differentiated. None of these criteria are sufficient whether taken in isolation or jointly. Temporality of the association is the only necessary causality criterion. Biological coherence can also be considered necessary with certain provisos (see above). Certain authors claim the very use of causality criteria is either useless or counter-productive (Lanes and Poole, 1984). Hill himself was very skeptical about the use of his criteria. Nevertheless, these criteria can be useful in the complex task of evaluating the plausibility that an association is causal by providing a grid to evaluate such plausibility.

Systems of classification of causal relationship plausibility

In order to propose concrete prevention measures in spite of the difficulties outlined above, systems to classify the degree of plausibility of possibly causal relationships have been proposed and put into practice. Such systems integrate elements akin to Hill's criteria. The two best known elements are cancer-related and emanate from the International Agency for Research on Cancer (IARC), which is affiliated to WHO (http://www-cie.iarc.fr/), and the United States Environmental Protection Agency (U.S. EPA) (1999).

For example, IARC experts regularly meet to pass judgment on the carcinogenic or non-carcinogenic nature of exposure to all kinds of substances present in the environment and publish these evaluations in the form of monographs. Both human and animal data are taken into account in order to agree on a general evaluation for each substance and assign it to a group in the five-level classification of plausibility that a substance is carcinogenic in man:

- Group 1: carcinogenic substance;
- Group 2A: probably carcinogenic substance;
- Group 2B: possibly carcinogenic substance;
- Group 3: unclassifiable substance;
- Group 4: probably non-carcinogenic substance.

In the first 80 monographs it has published (1972-2002), IARC has evaluated 878 substances and has classified 87, 63, 234 and 493 of these in groups 1, 2A, 2B and 3 respectively, and one in group 4. While these evaluations are of great value, it must be remembered that the elements taken into account are similar to Hill's criteria and are therefore subject to similar limitations.

In conclusion, establishing a causal relationship is useful both to further knowledge and propose public health prevention policies. It is, however, a very complex task. Hill's causality criteria are helpful in evaluating the causal nature of an association in spite of their many limitations and the impossibility of reaching a formal conclusion. Systems of exposure classification according to the degree of plausibility of a causal association have been formulated. They comprise elements similar to Hill's criteria and are commonly used.

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5

The environment and cancer: the contribution of toxicology

Over the last decades, a great deal of progress has been made in understanding the origins and mechanisms of cancer development. It is now accepted that cancer can have a genetic and environmental origin. The genetic component is well illustrated by the hereditary character of certain forms of cancer, family clusters and, in some cases, the identification of the genes responsible. Examples of this are certain types of colon cancer (HNPCC), a fraction of breast cancers (BRCA gene), and some thyroid cancers… (for reviews on the subject, see Foulkes, 2002; Sawyers, 2002; Ince and Weinberg, 2002; Green and Evan, 2002; Weber, 2002; Orsulic et al., 2002). It is worth noting, however, that genetic contribution is not limited to hereditary disease since a significant fraction of cancers is associated with one or more sporadic mutations.

Involvement of the environment in the occurrence of cancer has long been suspected. As early as the 18th century, the high frequency of scrotum cancers observed in chimney sweeps was associated with their professional environment (Pott, 1775). Over the last ten years, environmental involvement in the appearance of specific cancers has been established in a number of cases: tobacco and bronchiopulmonary cancer (Hecht, 1999), asbestos and mesothelioma (Britton, 2002), UV radiation and melanoma (Tucker and Goldstein, 2003), trichlorethylene and kidney cancer (Bruning and Bolt, 2000).

The effective role of the environment varies according to the various estimates but any divergence is mainly due to differences in the definition of environmental factors. One may nonetheless identify:

- The chemical environment (e.g. pesticides, dioxin);
- The physical environment (e.g. ionizing radiation, UV radiation, radon);
- Viral and bacterial infections, which can also give rise to several types of cancers.

Respective contributions of environment and heredity

The relative contribution of environmental and genetic factors in the appearance of cancer is not easy to determine. Studies carried out on thousands of Scandinavian twins have nevertheless permitted an appreciation of the relative contribution of the environment versus heredity in the genesis of different cancer types (Lichtenstein et al., 2000). The results of these studies have been confirmed in a study involving millions of individuals in Sweden and designed to evaluate the familial nature of many cancers (Czene et al., 2002). Other studies carried out on couples have also improved our knowledge on the origins of cancers and, in particular, the important contribution of life style (Hemminki et al., 2001).

The view that a clear distinction needs to be made between genetic mechanisms and environmental factors now appears far too narrow. Finally, various environmental

components can potentially interact: thus in third-world countries, the appearance of hepatic cancers is amplified by Hepatitis B viral infection, aflatoxin contamination and the genetic profile that determines the metabolism of this substance.

In summary, the origins of cancers must be examined according to cancer type and cancer localization while taking into account the interactions between genetic factors and the various components of our environment.

Various routes of contamination

The study of contamination via the environment must take several factors into account. Contamination can occur by ingestion, inhalation or transdermal absorption. In the case of chemicals, assessing true toxicity requires good knowledge of their distribution in the environment, routes of contamination as well as kinetic and dynamic properties in the organism.

The only pollutants discussed in the following presentation are chemicals. However, experts should also eventually study other environmental factors in a future collective expertise.

Classification of chemical pollutants

Chemical pollutants can either be classified according to structure or their probable mode of action. Both classifications present certain advantages.

Classification according to chemical structure is as follows:

- Aromatic polycyclic hydrocarbons (benzopyrene);
- Organochlorides and organobromides (pesticides, dioxin, PCB, polybromides);
- Aromatic amines;
- Organophosphorus compounds (sarin, chlorpyrifos);
- Nitrosamines;
- Fibers: asbestos;
- Heavy metals;
- Other compounds (toxins such as aflatoxin);
- Mixtures: tobacco, fine particles, tars.

Classification by major mode of action is as follows:

- Direct genotoxicants: physical agents, benzopyrene, aflatoxin;
- Non-genotoxicants: substances with their own cell signaling apparatus (dioxin-AhR receptor, pesticides-PXR receptor); endocrine disturbing substances (activation or inhibition of cell signaling, estrogen mimetic substances, organochloride pesticides); enzyme disturbing substances (organophosphorus compounds); cell stressors (oxidative stress, asbestos, metals, dioxin…);
- Indirect genotoxicants leading to cumulative toxicity (particles, asbestos, inflammation) or multiple toxicities (mixtures or non-mixtures).

The two classifications are of course not independent of each other but agents that are different in nature can clearly be genotoxic (radiation and xenobiotics, for example) while a particular type of agent such as organochloride pesticides can have various mechanisms of action.

Recent progress in the study of the mode of action of chemical pollutants

We are mainly interested here in advances in the field of non-genotoxic pollutants. Such pollutants activate different types of receptors that can be classified into two major categories: xenobiotics receptors *sensu strictu* (AhR receptors for dioxin and aromatic polycylic hydrocarbons, PXR receptors capable of linking drugs with pesticides, the CAR receptor the role of which remains to be elucidated with respect to environmental pollutants). The main function of such receptors is to allow the organism to adapt to xenobiotic influx since they are responsible for the induction of enzyme systems involved in elimination of xenobiotic substances. The second set of relevant receptors in terms of the environment is a group of receptors for endogenous substances – such as hormonal receptors – but nonetheless susceptible to modulation by polluting compounds (e.g. organochloride pesticides and the estradiol receptor). This is a case of "illegitimate receptor activation" leading to endocrine or metabolic disturbance (Figure 5.1).

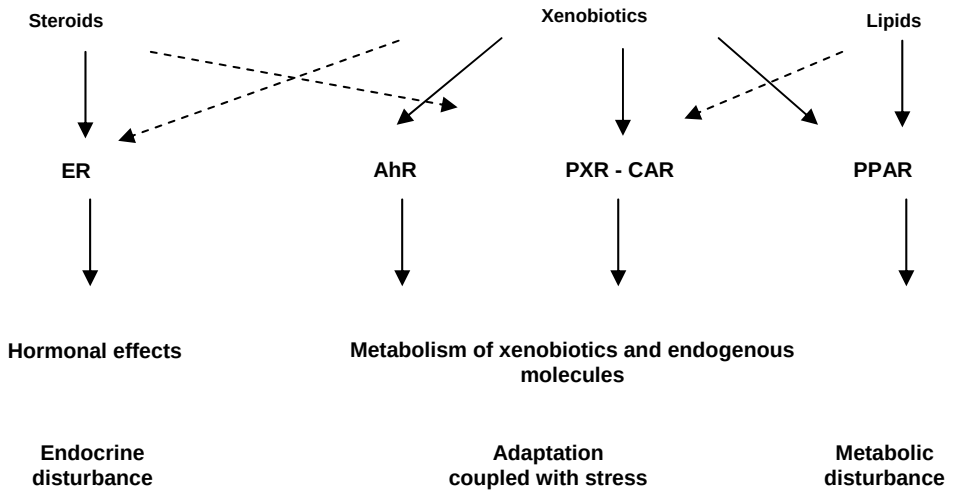

Figure 5.1: Legitimate and illegitimate xenobiotic receptors

It is interesting to note that toxicity can arise from interaction of a pollutant with its "legitimate" receptor (for example dioxin and the AhR receptor) as well as receptors for endogenous substances. It is also worth noting that the above receptor classification is oversimplified in that xenobiotic receptors can also bind endogenous substances (PXR receptors bind biliary acids, for instance). Finally, the concept of nuclear receptor affinity must be taken into account: the estradiol receptor has a 1 000-fold greater affinity for the natural hormone than for organochloride pesticides. In general, xenobiotics have moderate affinities for their receptors (on the order of the µM), which means it is necessary to verify the relevance of the results obtained; dioxin is the only substance that presents a strong affinity (on the order of the nM) for its receptor (AhR).

There are numerous models to study pollutant toxicity. There are also many *in vitro* or *ex vivo* as well as animal tests available. These tests are well characterized for genotoxic compounds even if the value of such tests is sometimes controversial. Studies on the mechanism of action

of non-genotoxic substances are not so well structured and depend on the expertise of each laboratory as well as the availability and relevance of animal and cellular models. It is important to emphasize that the mechanism of action of genotoxic and non-genotoxic compounds is different and that it is therefore hazardous to transpose knowledge relative to one of these categories to the other. This is particularly important with respect to mathematical models for predicting toxicity at low doses. Such models are often based on linearity of toxicity as a function of dose for genotoxic compounds but this is very controversial in the case of other compounds.

Nevertheless, recent studies are not so intent on separating genotoxic from non-genotoxic compounds. Numerous compounds that are not genotoxic induce an oxidative stress that can alter DNA and thus lead to genotoxicity (dioxin). Other compounds have themselves a non-genotoxic action while their metabolites are capable of forming DNA adducts (benzopyrene). The classical model of chemical carcinogenesis in rodents (initiator *versus* promoter) may be oversimplified under such conditions. Furthermore, the study of genic alterations in human tumors shows there is a succession of alterations leading ultimately to the appearance of cancers. Finally, apart from the effects on tumor initiation and promotion, pollutants might cause tumor progression and possibly facilitate cancer dissemination and metastases. The latter issue has unfortunately received little attention as a result of a lack of relevant experimental models.

What is the use of experimental toxicology?

The aim of studies in the field of health and the environment is to establish a relationship between an environmental factor and the appearance or the aggravation of cancer. Epidemiological studies are necessary and could in the first place focus on populations that are particularly exposed whether it is for professional, accidental or geographical reasons. The difficulty is then to generalize risk findings to the general population, which is subject to weaker exposure.

In order to establish such relationships, a major difficulty is to identify and measure exposure. Indeed, exposure may have occurred many years previously, in which case the challenge is to obtain reliable data on the quantity of exposure. There may also be residual quantities of a chemical or a persisting biological effect. This is a difficult step that weakens a large number of studies.

Furthermore, epidemiological studies can suffer from biases or lack sufficient power. Reported toxicity can be due to compound mixtures and it is difficult to know which of the substances or set of substances in the mixture is actually responsible for the effect.

Thus it is necessary to establish the biological plausibility of a carcinogenic effect in order to define the true incurred risk. The contribution of toxicology is not equivalent for all studies but it is unavoidable in situations where epidemiological criteria turn out not to be sufficiently powerful.

Toxicology and demonstration of mechanisms of toxicity also play an important role in the search for exposure markers, work on predicting toxic effects, and preventive action. In this respect, good knowledge of mechanisms of action also plays an economic role by helping prevent industry from spreading potentially dangerous substances.

To summarize, the experimental toxicological approach is useful:

- To establish the biological plausibility of the cause-effect relationship;
- As a predictive approach;

- As a public health preventive approach.

It also presents an obvious economic advantage for industry.

Difficulties associated with experimental toxicology

Studies on the mechanisms of action of a pollutant or an environmental factor are carried out using model systems. Animal models are often used but their relevance to the human situation is sometimes controversial or poorly established. *Ex vivo* or *in vitro* models derived from human samples are also used but criticized precisely for not being whole organism studies. It is often necessary to have an array of arguments to confirm the relationship between the biological properties of an environmental factor and its role in the appearance of cancers.

One must nonetheless emphasize that knowledge on the mode of action enables one to know better whether observations made on animals can be transposed to man. Examples of relative failure with animal models clearly illustrate this point (Meek et al., 2003).

For instance, the renal carcinogenicity of limoneme in male rats is linked to its binding to the alpha-2-microglobulin protein. Now, this protein is specifically found in rats and has no equivalent in man. This animal model is therefore not transposable.

Peroxysome proliferators are potent hepatic carcinogens in rodents but fibrates are not carcinogenic for man. This difference can be explained by a discrepancy in the number of receptors (PPAR receptors) for such compounds between man and rodents. Furthermore, human and rodent PPAR receptors seem to have distinct, sometimes diametrically opposed, genic effects.

Dioxin is a potent carcinogen for certain rodent strains while its effect in man is relatively moderate. Now, in sensitive rodent strains, the affinity of the AhR dioxin receptor for this pollutant is 10 to 100 times higher than the affinity for the corresponding human receptor, which explains the observed difference in sensitivity.

Thus better knowledge of the mode of action enables one to judge more competently the relevance of an animal or cellular model for testing the toxicity of a given pollutant in humans.

New methodologies

Experimental toxicology can certainly benefit from new technologies in genomics, proteomics and metabonomics. Such large-scale approaches should help get a better understanding of mechanisms of action, compare effects in different species, provide new biological markers and contribute to developing predictive toxicology. Other useful technologies are analytical methods for the dosage of pollutants as well as transgenic approaches aimed at "humanizing" animal models (e.g. mice models) to make them closer to the human situation and improve the possibilities of transposing results from animal to man.

Questions and future challenges for experimental toxicology

In spite of recent progress, numerous issues of interest for other fields of activity in the area of health and environment remain unresolved. We ought to be able to understand and predict more efficiently the effects of chronic exposure to low doses of pollutants, which remain an unresolved problem for cancer in particular. We should have more insight into the effects of mixtures since most contaminations are multiple in nature. While we are beginning to understand the mode of action of certain pollutants, we still know very little about the

effects of mixtures and about the interactions between modes of action (synergy, opposite effects or independence). This is crucial for contaminants that are often present in conjunction (pesticides and dioxin) or for contaminants associated with particles (atmospheric particle constituents). Finally, numerous pollutants seem to have multiple effects and rather than being content with the first mechanism of action unveiled, we must explore the whole range of possible mechanisms (for example the metal cadmium is also an endocrine disturbing substance). Recent studies also indicate that even when different pollutants have the same receptor, their effects may diverge in as much as the mode of activation of the receptor depends on the nature of the ligand.

In conclusion, experimental toxicology is an essential research link in the field of cancer and environment. It cannot replace epidemiology for demonstrating the relationship between pollutant and cancer pathology but can make an important contribution by establishing biological plausibility. Other applications of the experimental approach are the reinforcement of predictive toxicology, the development of exposure markers and improved definition of sources. However, such applications must not eclipse the importance of this discipline for extending our knowledge.

Numerous questions remain to be answered through this experimental approach, particularly with respect to low doses, mixtures and complex modes of action. New technologies should help answer pending questions.

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6

Genetic susceptibility factors in cancer

Cancer development is a multi-step process requiring the transformation of a normal cell into a pretumoral and/or tumoral cell. The large number of mutations encountered in certain tumor cells suggests that these cells have become genetically unstable and that this instability is associated with dysfunction of the genes involved in regulating the cell cycle ("gatekeepers") and/or ensuring faithful transmission of genetic information ("caretakers") (Kinzler and Vogelstein, 1997). In the first case, the genes that have lost their normal regulatory role are proto-oncogenes or tumor suppressor genes. In the second case, genes that are generally involved in repair no longer ensure proper maintenance of genetic integrity. The above concepts are often derived from studies of family cancers, which have made it possible to show the existence of such genes. Thus, retinoblastoma or Li-Fraumeni syndromes, and familial predisposition to breast or colon cancer have lead to the isolation and characterization of certain tumor suppressor genes. *Xeroderma pigmentosum* (a deficiency in enzymes involved in nucleotide excision repair), HNPCC (Hereditary Non-Polyposis Colorectal Cancer: a deficiency in enzymes involved in mismatch repair), Bloom's syndrome (a deficiency in BLM helicase, which ensures faithful recombination), have made it possible to characterize DNA repair enzymes. Familial cancers and pathologies that strongly predispose to cancer represent approximately 5 to 10% of all cancers (Nagy et al., 2004).

Most common forms of cancer (sporadic cancers) probably result from effects of multiple genetic variants of modest impact (Single Nucleotide Polymorphisms[6] or SNPs) and other risk factors (life style, occupational exposure...). SNPs can have a strong impact at the population level if their frequency is high. For instance, 20% of cancer cases can be attributed to weak-effect polymorphism (OR=1.5) with a high prevalence (50% of the population). This attributable proportion is the same as that of a gene that confers a high risk (OR=5) with a low prevalence (5% of the population) (Brennan, 2002).

SNPs-cancer associations

Particular attention was initially given to SNPs of genes involved in the metabolism of toxic chemicals (conversion of toxic chemicals into intermediate metabolites by phase I enzymes such as cytochromes P450 and detoxification by phase II enzymes such as glutathione transferases and N-acetyltransferases). Other genes that can influence the risk of cancer, such as those involved in DNA repair, immunity, cell cycle control, or toxic substance dependency, are currently being studied. A preliminary list of candidate genes is given in Table 6.I.

[6] Genetic variant with a frequency of at least 1% in the general population

Table 6.I: Preliminary list of genes that might influence the development of cancer (from Brennan, 2002)

Type of gene	Genes
Metabolism (Phase I)	CYP1A1, CYP1A2, CYP2A6, CYP2D6, CYP2E1, ADH2, ADH3, MPO, mEH
Metabolism (Phase II)	GSTM1, GSTT1, GSTP1, NAT1, NAT2, ALDH2, NQO1, SULT1A1, SOD2
DNA repair	XRCC1, XRCC3, XPD, XPF, ERCC1
Role in immunity	IL1A, IL1B, IL2, IL6, TNF, HLA class I/II
Cell cycle control	TP53, HRAS
Dependency to nicotine and other receptors	CYP2A6, DAT1, DRD2, DRD4, RARA

Results of hundreds of epidemiological studies (essentially case-control studies) on various cancers have been published over the last ten years. In spite of this sizeable effort, the results in terms of acquired knowledge are rather disappointing in that the positive associations found have not always been confirmed. The relatively small size of the populations studied (generally 100 to 300 cases) and lack of statistical power to demonstrate modest effects (ORs below 1.5) could in part explain the discordance between results. Indeed, estimates of the number of subjects necessary to detect ORs between 1.2 and 1.5 with a statistical power of 80% indicate that 500 to 2.000 cases (and an equal number of control subjects) are necessary with a prevalence of exposure to the factor under scrutiny (e.g. genetic polymorphism) of 50% in the general population (Figure 6.1) (Brennan, 2002).

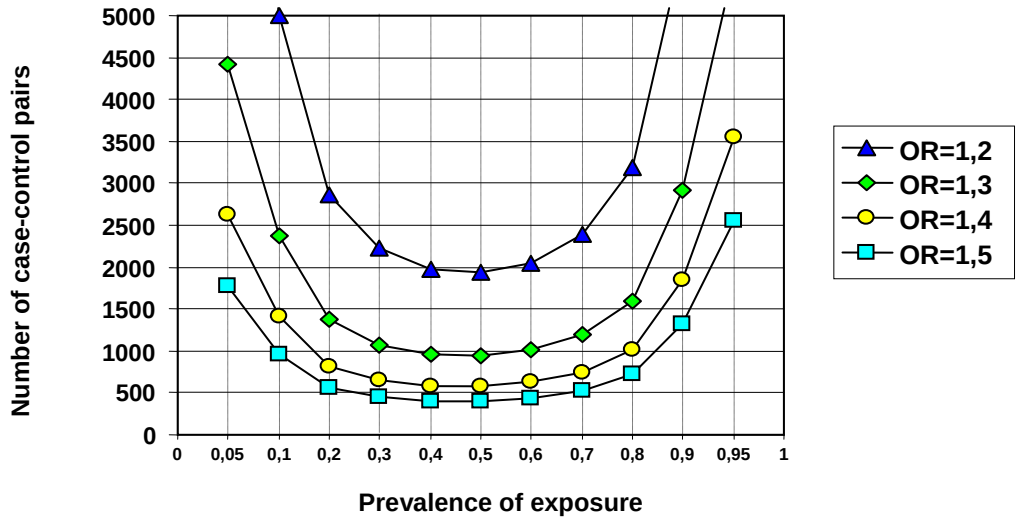

Figure 6.1: Necessary sample size to demonstrate the presence of a weak OR (≤1.5) as a function of prevalence of exposure (power=0.80, α=0.05)

Numerous synthetic studies (systematic reviews of the literature and meta-analyses of published studies) have been carried out in order to evaluate the relationship between specific SNPs and certain cancers (Houlston and Peto, 2004). However, few of them have made it possible to demonstrate the existence of significant associations (breast cancer and CYP2C19-$(TTTA)_{12}$, GSTP1-Ile105Val and TP53-Arg72Pro; colon cancer and APC-I130K, MTHFR-Ala677Val and HRAS-VNTR; cancer of the bladder and NAT2-slow acetylator and GSTM1 deletion; cancer of the lung and GSTM1 deletion) (Table 6.II).

Table 6.II: Significant SNPs-cancer associations demonstrated by synthetic studies (from Houlston and Peto, 2004)

Cancer	Polymorphism	OR [95% CI]	Number of studies	Total number of cases	Reference
Colorectal	APC I130K	1.77 [1.30-2.41]	3	670	Houlston and Tomlinson, 2001
	HRAS1-VNTR	2.50 [1.54-4.05]	5	394	Houlston and Tomlinson, 2001
	MTHFR Ala677Val	0.77 [0,64-0,93]	4	1 949	Houlston and Tomlinson, 2001
Breast	CYP19(TTTA)12	2.33 [1.36-4.17]	3	1 404	Dunning et al., 1999
	GSTP1 Ile105Val	1.60 [1.08-2.39]	2	172	Dunning et al., 1999
	TP53 Arg72Pro	1.27 [1.02-1.59]	3	412	Dunning et al., 1999
Bladder	NAT2	1.40 [1.2-1.6]	22	2 496	Marcus et al., 2000
	GSTM1 deletion	1.44 [1.23-1.68]	17	2 149	Engel et al., 2002
Lung	GSTM1 deletion	1.17 [1.07-1.27]	43	7 463	Benhamou et al., 2002

Gene-environment interactions

Taking into account genetic factors in the study of cancer-environment relationships could help identify different risk levels in exposed sub-groups of individuals. A well-documented example of this is the risk of bladder cancer and exposure to aromatic amines as a function of NAT2 genotype (fast and slow acetylators). Differences in cancer risk have been observed according to NAT2 genotype; thus, not taking into account this genetic factor in studies on the relationship between cancer of the bladder and aromatic amines leads to average and therefore diluted risk estimates. A recent review of the literature (Kelada et al., 2004) indicates that a certain number of genetic polymorphisms could modify the risk of cancer associated with environmental or occupational exposure (Table 6.III).

Table 6.III: SNPs that could modify the risk of cancer associated with environmental or occupational exposure (from Kelada et al., 2004)

Exposure	Cancer	Gene(s)
Alcohol	Esophagus	ALDH2
Aflatoxin B1	Liver	GSTM1, EPHX1
Heterocyclic amines	Colon	NAT2
	Breast	NAT2, SULT1A1
Aromatic amines (dye industry)	Bladder	NAT2
Halogenated solvents (e.g.TCE)	Kidney	GSTT1
Pollution (HPAs)	Lung	GSTM1
Solar radiation (UV)	Skin (BCC)	XPD
Tobacco	Lung	CYP1A1, GSTM1, NAT1, NAT2, EPHX1, XRCC1
	Bladder	CYP1A2, NAT2, GSTM1
Passive smoking	Lung	GSTM1

It is however necessary to point out that interaction studies between two genetic factors or between a genetic factor and an environmental factor generally require large numbers of subjects, on the order of several thousand cases and controls.

Means of calculating the interactions between two dichotomic factors (present/absent) are given in Table 6.IV, according to whether the studies involve cases with or without controls (Botto and Khoury, 2004).

Table 6.IV: Means of calculating the interactions between two dichotomic factors (from Botto and Khoury, 2004)

G	E	Cases	Controls	OR		Contrast	Main information
+	+	a	b	ah / bg	A	A *versus* D	Joint effect of G and E *versus* nothing
+	-	c	d	ch / dg	B	B *versus* D	G only *versus* nothing
-	+	e	f	eh / fg	C	C *versus* D	E only *versus* nothing
-	-	g	h	1	D		Baseline

Other measurements	OR	Main information
OR for cases	ag / ce	Deviation relative to a multiplicative model of interaction
OR for controls	bh / df	Independence of factors E and G in the population
Multiplicative interaction	A / (B*C)	Deviation relative to a multiplicative model
Additive interaction	A - (B+C-1)	Deviation relative to an additive model

G: dichotomic genetic factor (present/absent)
E: dichotomic environmental factor (present/absent)

In conclusion, the studies carried out to date have generally analyzed a relatively restricted number of polymorphisms. Recent advances in the identification of new variants and high-throughput genotyping techniques should facilitate the simultaneous analysis of a large number of polymorphisms single genes and multiple genes within a single pathway. However, the simultaneous study of a large number of polymorphisms requires samples of considerable size. Furthermore, the large quantity of genotypic data generated in this way requires the development of new statistical methodology.

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7

Dose-response relationship and analysis of cancer risks

In experimental animal studies, the subjects analyzed only differ theoretically in that they are or are not exposed. The effect observed in those that are exposed is therefore solely attributable to exposure. The only causality problem posed in such experiments is result reproducibility.

In epidemiology, which is a science based on the observation of people and populations (where the statistic unit is not the individual but a population), the individuals analyzed have had and still have a huge variety of behavior and genetic profiles that are impossible to describe and take into account in detail. As a result, one cannot reduce the terms of the comparison between exposed and unexposed individuals to sole exposure difference.

Whether an epidemiological approach is used to improve existing knowledge or to provide a basis for public health policy, judging causality in a relationship between exposure and effect is crucial. The basic proposition of a causality judgment is as old as etiological epidemiology itself and Hill's criteria (1965) remain on the whole relevant today (Table 7.I).

Table 7.I: Hill's criteria (1965) and examples of applications

Criteria	Leukemia and ionizing radiations	Cancer of the larynx in uranium miners
Strength of association	+	+
Dose-effect relationship	+	-
Temporal sequence	+	+
Specificity	-	-
Consistency of results (reproducibility)	+	-
Biological plausibility	+	+/-
Biological coherence	+	+/-
Experimental evidence	+	-
Reasoning by analogy	+	+

Without examining each criterion in great detail, it is worth emphasizing all the criteria need not be fulfilled in order to judge that causality is present (for instance there is no doubt about the leukemogenic effect of ionizing radiation). Furthermore, such criteria are relative, i.e. validated criteria become more important in as much as others are invalidated. There are, however, two exceptions. First of all, it is hard to imagine in the case of the relationship of temporality how the effect could precede the cause. Second, when applied to epidemiology, the scientific rule of result reproducibility demands that no causality judgment be ever made on the sole basis of an isolated study, however excellent. Finally, judgment is passed on the basis of available elements and it would be nonsense to try and give a generic numeric weight to each of the criteria to calculate a score that would decide in favor of causality by reference to a threshold value. For example, one might be tempted to give more weight to a strong association suggested by a high relative risk that was statistically very significant.

However, associations are often weak in the case of environmental exposure and one might risk never reaching a conclusion of causality in such instances. Conversely, the example of uranium miners exposed to radon, a radioactive gas of natural origin (causally!) responsible for lung cancer, shows the hazards of lending too much weight to high relative risk. In this particular case, one observed a strong association in the cohort of French miners but no significant association in ten other cohorts using a very similar protocol. It was therefore concluded there was no causal link between this pathology and the circumstances of exposure. It is also worth noting that the criterion of existence of a dose-response relationship (Hill refers to a biological gradient) supposes a rising monotonic curve. For a more detailed discussion of Hill's criteria, the reader is referred to Chapter 4.

Dose-response relationship, an element that determines priorities

Concluding there is a causal link between exposure to a given agent and the occurrence of a disease is a necessary but not sufficient condition to determine action priorities. To do this, one also needs to know who is exposed and to what extent, which involves descriptive epidemiological studies, and to determine the effect of a given amount of exposure or dose of a particular carcinogen, i.e. the dose-response relationship.

Mutagenic or genotoxic carcinogens

The most distinguished international committee experts, particularly those dealing with radioprotection issues (International Commission on Radiological Protection) consider that the mode of action of genotoxic carcinogens (mutagenic or responsible for chromosomal abnormalities) does not involve a threshold. The arguments in favor of this hypothesis are presented below.

According to this model, any dose of a genotoxic carcinogen is responsible for an excess of cancer risk. One of the major challenges then is to determine the shape of the dose-response curve at low doses. Indeed, the majority of the population is usually exposed to low doses. The problem is that the effects of low doses are very subtle and cannot be observed. One must therefore extrapolate from observable data what is likely to occur in the non-observable domain (Figure 7.1). In order to do this, one can use epidemiological data when it is available, which is rather rare, or experimental data on animals, which is more frequently the case. Either way, different mathematical models of extrapolation can generally adjust satisfactorily to the data in the observable domain (Figure 7.2). The quality of such adjustment is judged on the basis of a statistical test of adequateness. However, the shape of the dose-response curve outside the observable domain is both determined on the basis of the observable data used by the models and impossible to validate. Figure 7.3 shows the results of animal data extrapolation for the risk of death by cancer after dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin) administration. Though several models adequately adjust to the data, the risk estimates provided by each of them for a given dose vary widely, particularly as the dose level is reduced. In the first instance, the American Protection Agency (U.S. EPA) proposes using the so-called linearized multistage or LMS model – provided it is sufficiently adequate for the data used – for two reasons. First, because it is partially based on biological considerations in accordance with current ideas on carcinogenesis mechanisms; and second because it generally gives rise to the most pessimistic risk estimates, which affords extra precaution. It is worth noting that this is not the case for the example given in Figure 7.3 for curves labeled MS or MS_2, the latter case corresponding to a truncated set of data in order to ensure better adequateness.

In conclusion, the choice of model is a parascientific decision that involves considerations such as principles (to be as protective as possible), knowledge or hypotheses on mechanisms of action and mathematical modelization tools.

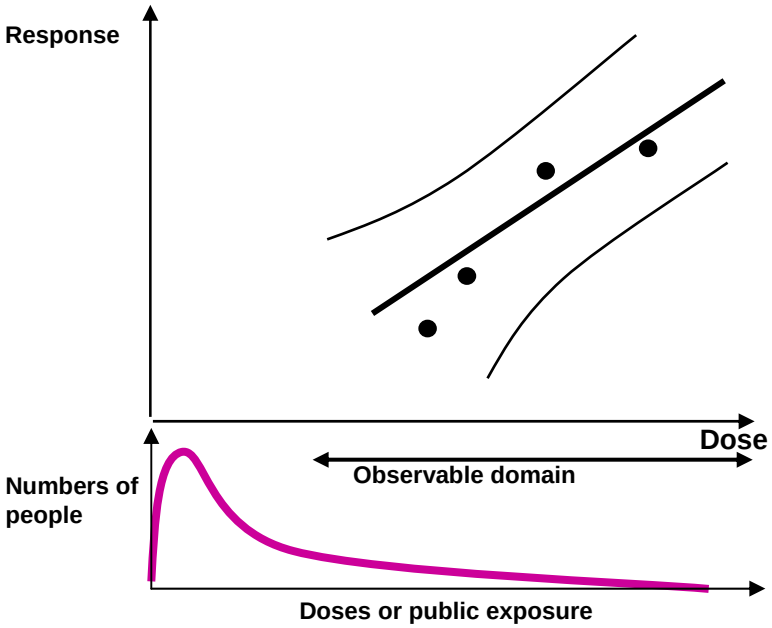

Figure 7.1: Observable domain and common distribution in cases of public exposure

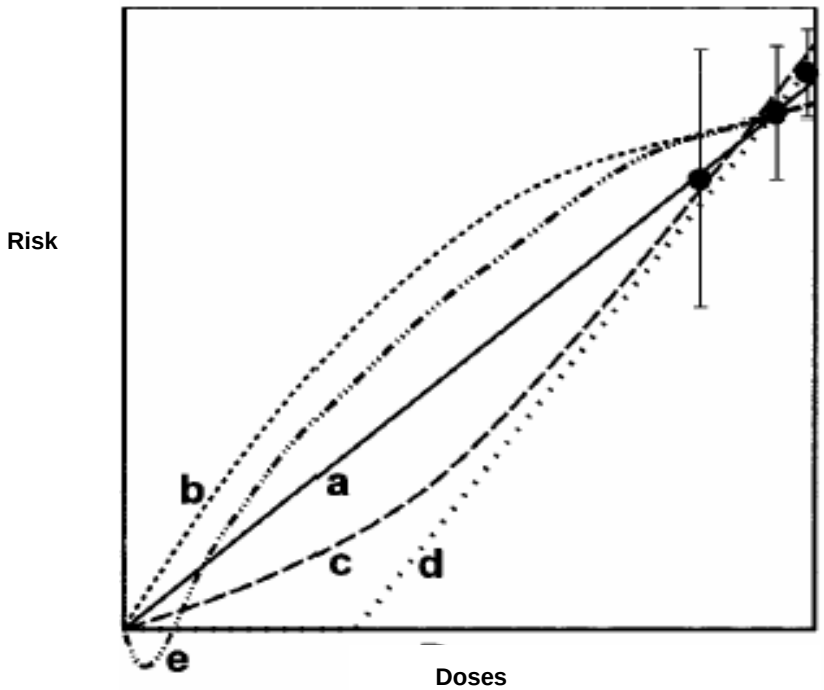

Figure 7.2: Diagram of the possible extrapolations from measured risks at very low doses (from Brenner et al., 2003)

Central tendency risk measurements are represented here by black circles with the corresponding confidence intervals. All the models used fit the observed experimental or epidemiological data. a: linear extrapolation; b: supralinear; c: sublinear; d: threshold; e: hormetic (the risk decreases at low doses)

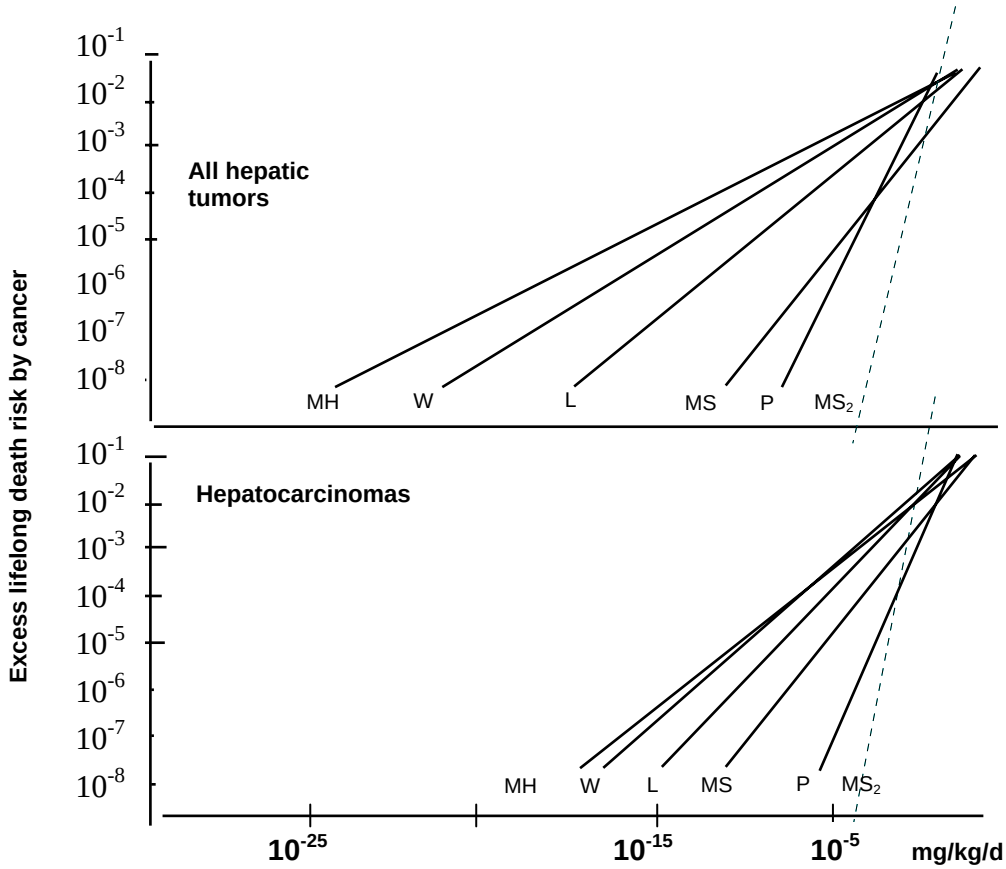

Figure 7.3: Applying different extrapolation models to a set of animal data (from Longstreth and Hushon, 1983)

Excess death risk by cancer in the case of 2,3,7,8-tetrachlorodibenzo-p-dioxin

M: Multi-hit; W: Weibull; L: Logit; MS: Linear multistep; P: Probit; MS_2: Linear multistep applied to truncated set of data (shown as a dotted line)

Non-mutagenic or non-genotoxic carcinogens

For carcinogens intervening at stages other than the initial stage of mutagenesis (e.g. at the promotion or progression stage), it is now accepted that there is a dose threshold below which there is no effect. The value of the threshold now remains to be determined. This can sometimes be done on the basis of epidemiological studies (Figure 7.4). However, it is more often than not obtained from experimental studies on animals such as rodents. For a given effect, the value of the threshold dose of the agent responsible varies according to experimental conditions. On the one hand, the species tested and the particular strain used have a specific sensitivity to the tested carcinogen. On the other hand, the statistical power of the study influences the dose threshold observed, which can be lower if the statistical power is increased by using more animals per dose group. It is therefore necessary to judge in this case which value ought to be chosen and whether the transposition of animal data to the human species is plausible. Once again, one is faced with having to pass judgment and make a decision on the basis of scientifically established data but under circumstances involving a measure of uncertainty.

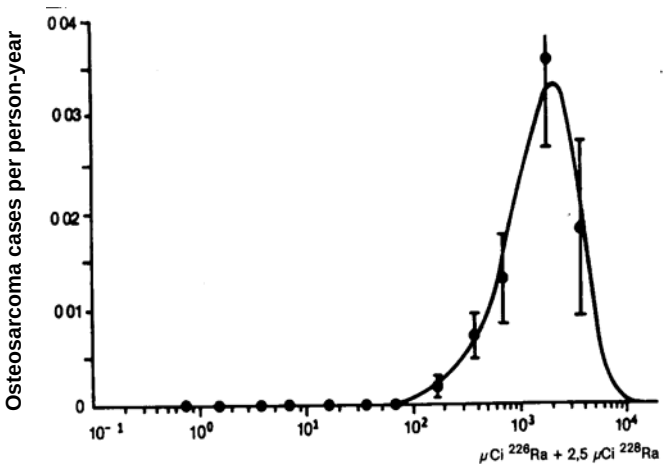

Figure 7.4: Threshold effect: epidemiological observation in the case of radio-induced osteosarcoma in women workers having used radium-based luminescent paint (from Bertin, 1991)

Complete carcinogens

A molecule can clearly be non-genotoxic after having been tested using a battery of state-of-the-art *in vitro* tests (for example the Ames test for mutagenicity, sister chromatid exchange for genotoxicity…), yet be an avowed carcinogen acting at the promotion stage. Such a promoter can only exert its promotional action if the necessary initial damage to the genetic material has already taken place. However, some promoters can sometimes induce cancers without prior exposure to an initiator when administered to animals in the course of *in vivo* carcinogenic studies. A well-known example of this is dioxin (Kociba et al., 1978; Holder and Menzel, 1989). In view of this, it is necessary to pass judgment whether to consider the dose-response relationship for such an agent as having or not having a threshold. In the case of dioxin, the U.S. EPA considers on the basis of empirical observation that this molecule is a "complete" carcinogen for which there is no threshold of action. The majority of international committees of experts judges it on the basis of its promoter mechanism of action and therefore considers there is a threshold.

Risk projections

Observations can also permit impact estimates by testing one or more models that will serve to predict the shape of the dose-response curve as a function of the dose received as well as the incidence of and mortality by a given cancer in the population in the absence of exposure (baseline risk). This approach can be useful to estimate lifelong risk in a cohort for which one wishes to determine risk after exposure while significant numbers of the subjects followed are still alive and free of cancer. The projection model may be multiplicative (relative risk model) with respect to the baseline risk or additive (constant risk model). The exposure impact is clearly different according to the model chosen (Figure 7.5).

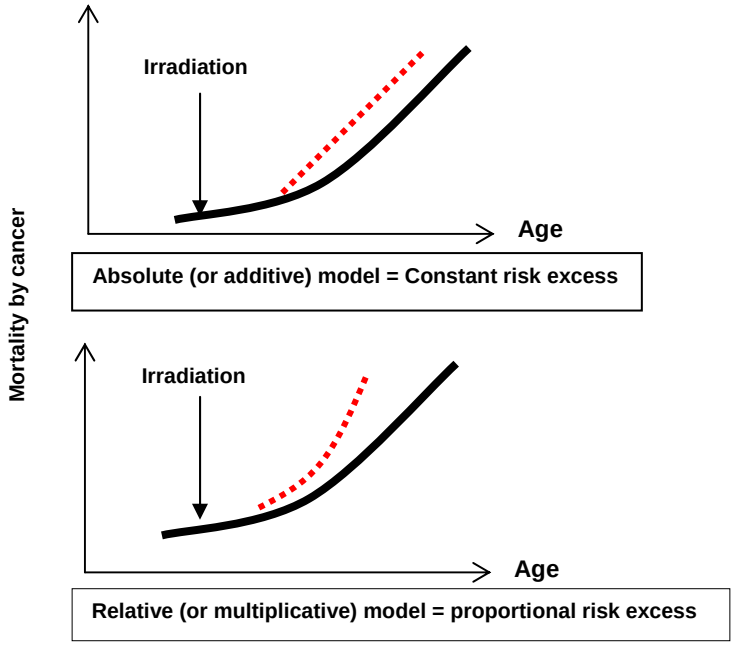

Figure 7.5: Risk projection models. Evolution of mortality by cancer as a function of age: without exposure (thick line) and with exposure (dotted line)

Overall effect of the existence of sensitive sub-populations on the dose-response relationship

For breast cancer linked to ionizing radiation exposure (Brenner et al., 2003), there is among the general population a very small proportion (about 0.25%) of women that are highly sensitive – for genetic reasons in particular – to the effect of genotoxic carcinogens, yet the dose-response relationship is linear at low doses for these subjects just as it is for the general population. When the dose increases, the number of cancers among sensitive women reaches a plateau (all these women will develop cancer). For the two populations put together, the curve will be overall supralinear (Figure 7.6). In this case, applying a linear relationship for the exposed population as a whole, including highly sensitive women, will underestimate the risk.

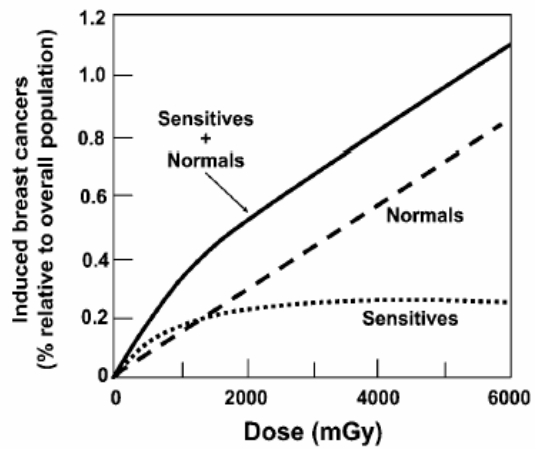

Figure 7.6: Dose-response relationship for breast cancer risk linked to ionizing radiation exposure for a population of women including a very small proportion (0.25%) of extremely sensitive subjects (from Brenner et al., 2003)

Transpositions, extrapolations, analogies

In the case where risk is projected, if the risk projection extrapolated from last follow-up data is compatible with a proportional risk model, the estimated risk for a given dose is going to depend on baseline incidence or mortality, which varies from one population to another and has a noticeable influence. Table 7.II helps appreciate the problem by giving a few examples of differences in death rates between countries for three cancer localizations.

Table 7.II: Standardized death rates per 100.000 for various cancers in 1988

	Lung (M+F)	Breast (F)	Stomach (M+F)
United States	53	32	6
Japan	25	8	41
Great Britain	57	42	16
France	32	27	10

Indeed, the general issue is whether one can justifiably transpose observations made on one population to another population in the observable domain. For example, is the dose-response relationship observed for breast cancer risk due to ionizing radiation in survivors of the Hiroshima and Nagasaki atomic bombing valid to estimate the exposure risk of the French population to the same radiation 50 years later? There is no simple answer to this question except to say that the further away we move in time or space, the greater the uncertainty. Once more, it is necessary to exercise judgment since elements confirming the comparability of different populations are lacking.

Lack of epidemiological data makes the problem even more acute when transpositions must be made from animals to man. Knowledge about mechanisms of action and their phylogenetic conservation is in this case an important, though rarely decisive, guide.

Finally, a particular variety of transposition is what Hubert (2003) in the wake of Hill (1965) calls an analogy, when one supposes, for example, that an effect observed after exposure by inhalation might also occur when the same agent is ingested. Figure 7.7 summarizes the various transpositions discussed.

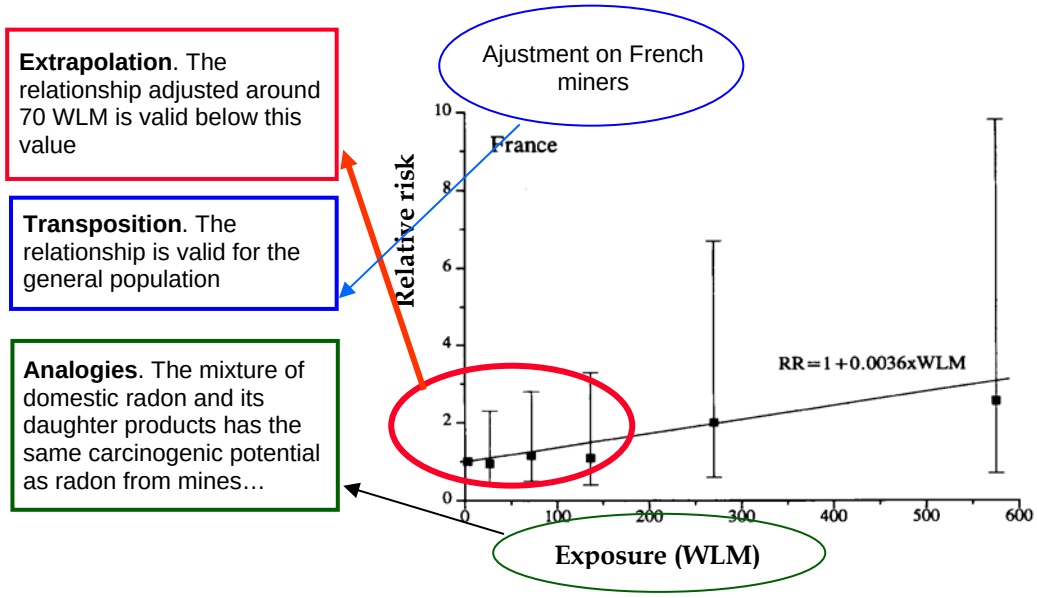

Figure 7.7: Example of possible gain from transposition/extrapolation/analogy in the case of radon exposure (from Hubert, 2003)

Inferences from data on French uranium miners for the French population as a whole

Controversy about linearity without a threshold

The existence of DNA repair mechanisms is well established. To put it simply, a mutation can only be stable when there is concomitant damage to the two complementary DNA strands. At very low dose, some authors argue the probability of such concomitant damage is nil since the agent concentration at the relevant chromosome site is bound to be insufficient, which means there must always be a threshold. There is a controversy as to whether such conclusions are justified (Brenner et al., 2003) but the pros and cons cannot be discussed in detail here. In any case, the problems of extrapolation and transposition discussed above are also relevant here. In other words, demonstrating the existence of a cellular or pluricellular threshold poses the problem of knowing if such a threshold exists at the organism and population level (in the case of highly sensitive populations) and if so, of determining its value. We are far from being able to estimate such a threshold on solid grounds and there is really no operational alternative to the pragmatic approach, which uses the linearity model without a threshold.

In conclusion, the shape of the dose-response curve contributes to making a causality judgment and, if the latter is deemed justified, determining sanitary impact and action priorities provided the exposure distribution is known for the target population. In any case, this approach deals with single carcinogens and cannot in practice take into account multiple exposures. It is also important to emphasize that qualitative and quantitative uncertainties are such that evaluation of the dose-response relationship, while based in as much as possible on well-established scientific facts, remains a question of judgment.

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8

Attributable risk

Once the carcinogenicity of an environmental agent has been established, the major question is to assess the real impact of this agent on the occurrence of cancer at the population level. In public health, knowing what this impact represents allows one to judge the relevance of the primary prevention measures aimed at reducing or eliminating population exposure to such an environmental carcinogen. The impact is therefore a fundamental element that can guide public health decision-makers in establishing priorities for primary prevention. It also allows the scientific community and general public to answer questions as to the true weight of a supposed or established carcinogen in the occurrence of cancer cases or its possible responsibility in the increase in certain types of cancers in the population. Different measures of impact have been defined to evaluate the contribution of one or more exposure factors, whether environmental, behavioral, nutritional, medicinal or otherwise, to the development of new cases of a particular disease in the population. Such measures depend not only on the strength of the association between the exposure factor under consideration and the disease studied but also on the prevalence of this factor in the population as a whole or various sub-groups of this population. Apart from very special circumstances outlined below, such measures quantify a potential impact at the population level, which may be distinct from the real impact. The most commonly used measure of impact is the attributable risk. This measure and the corresponding term "attributable risk" (AR) were initially proposed by Levin in 1953 (Levin, 1953) in order to quantify the impact of tobacco consumption on the occurrence of lung cancer at the whole population level. It was then progressively applied to all types of exposures and pathologies.

Definition and generalities

Attributable risk is defined by the following ratio:

$$AR = \{Pr(D) - Pr(D \mid \bar{E})\} / Pr(D) \quad (1)$$

The numerator is equal to the difference between two probabilities, the overall probability of the disease, Pr(D), in the population (generally made up of both exposed, E, and unexposed subjects, $\bar{E}$) and the hypothetical probability of the disease in the same population supposing exposure was totally eliminated, Pr($D \mid \bar{E}$). It therefore quantifies the additional probability of the disease in the population associated with the presence of the exposure factor. The attributable risk AR measures the corresponding proportion relative to the overall probability of disease in the population. Such different probabilities correspond to disease risks (probabilities of developing the disease in the course of a given lapse of time) but, under certain conditions or in the case of certain applications, disease incidence rates may be substituted to risks in order to define the attributable risk.

Others formulations as a function of the prevalence of exposure and the strength of association

Unlike measures of association such as relative risk (ratio of disease risks in exposed and unexposed subjects), attributable risk depends both on the strength of association between the exposure factor and the disease and the prevalence of this factor in the population, p_E. This joint dependency becomes apparent if the formula (1) is rewritten as follows. Pr(D) can be expressed as:

$$\Pr(D|E)\,p_E + \Pr(D|\overline{E})\,p_{\overline{E}} \quad \text{where} \quad p_{\overline{E}} = 1 - p_E$$

in both the numerator and denominator. Now,

$$\Pr(D|E) = \mathrm{RR} \times \Pr(D|\overline{E}),$$

where RR represents the relative risk (or the ratio of incidence rates of the disease in exposed and unexposed subjects). Because the term $\Pr(D|\overline{E})$ cancels out, the attributable risk AR can be written as follows (Cole and MacMahon, 1971; Miettinen, 1974):

$$\mathrm{AR} = \{p_E\,(\mathrm{RR}-1)\} \,/\, \{1 + p_E\,(\mathrm{RR}-1)\} \qquad (2)$$

i.e. both as a function of the exposure prevalence in the population, p_E, and of relative risk (or ratio of incidence rates), RR.

An alternative formulation emphasizes this joint dependency. By expressing Pr(D) and Pr($D|E$) as shown above, the numerator of formula (1) can be rewritten as follows:

$$p_E \Pr(D|E) - p_E \Pr(D|E) / \mathrm{RR}.$$

Using Bayes's theorem, one can express Pr($D|E$) as $\Pr(E|D)\Pr(D) / p_E$, which leads to the following expression for the numerator of formula (1):

$$\Pr(D)\,p_{E|D}(1 - 1/\mathrm{RR})$$

thus giving the following (Miettinen, 1974):

$$\mathrm{AR} = p_{E|D}\,(\mathrm{RR}-1) \,/\, \mathrm{RR} \qquad (3)$$

i.e. both a function of the exposure prevalence in subjects suffering from the disease under consideration (cases), $p_{E|D}$, and of relative risk (or ratio of incidence rates), RR.

Thus according to the exposure prevalence, a high relative risk value may give rise to a high or low attributable risk value, which leads to very different consequences in terms of public health. One of the consequences is that attributable risk is generally not portable from one population to another since exposure prevalence can vary extensively between different populations in time and space. This situation differs from that observed for measures of association, which are generally much more readily portable from one population to the next because the strength of an association is in most cases subject to little variation between populations except when the exposure factor strongly interacts with environmental or genetic factors specific to the various populations.

Range

When the exposure factor under consideration is a risk factor (RR>1), it follows from the above definition that the attributable risk lies between 0 and 1. Consequently, it is frequently expressed as a percentage. The value of the attributable risk increases both with the strength of the association between the exposure under consideration and the disease studied,

measured by the quantity RR, and the exposure prevalence in the population. To an exposure prevalence of 1 (or 100%) corresponds an attributable risk value given by the quantity (RR-1)/RR. Furthermore, the value of the attributable risk tends toward 1 when the relative risk (or ratio of incidence rates) tends toward an infinitely high value provided exposure is present in the population (i.e. for an exposure prevalence that is not equal to zero).

The attributable risk is equal to zero in the absence of association between exposure and the disease (RR=1) or in the absence of exposure in the population. Negative values of attributable risk are possible for a protective exposure (RR<1). In this case, attributable risk values can go from 0 to -∞, on which scale interpretation is arduous. A possible solution is to reverse the coding for exposure by exchanging the exposed and unexposed categories and return to a situation where attributable risk is once again positive. An alternative solution is to consider another measure of impact, i.e. the preventive or prevented fraction (see below).

Terminology and synonyms

Some degree of confusion has arisen in the terminology used as a result of reported use in the literature of no less than 16 different terms to designate attributable risk (Gefeller, 1990, 1995). Nevertheless, a recent bibliographical search (Uter and Pfahlberg, 1999) reported a relative coherence in the terminology used, the terms "attributable risk" and "population attributable risk" (MacMahon and Pugh, 1970) being by far the most commonly used, followed by the term "etiological fraction" (Miettinen, 1974). The terms "attributable risk percentage" (Cole and MacMahon, 1971), "fraction of etiology" (Miettinen, 1974), and "attributable fraction" (Ouellet et al., 1979; Last, 1983; Greenland and Robins, 1988; Rothman and Greenland, 1998) are less common. Other terms are very rarely used.

It is worth emphasizing another possible source of confusion in the terminology because of the – happily rare – use by certain authors (MacMahon and Pugh 1970; Markush, 1977; Schlesselman, 1982) of the term "attributable risk" to designate a measure of association called the excess incidence and defined as the difference between incidence rates of exposed and unexposed subjects, rather than a measure of impact. However, ambiguities can usually be resolved by context.

Use and interpretation

Attributable risk is used in order to quantify the impact of primary prevention policies relative to the disease under study or to quantify the fraction of disease that can be explained by known factors. There follows two types of interpretations.

Impact of primary prevention of disease

While measures of association such as relative risk or the odds ratio (ratio between disease risk over its complement to 1 in exposed subjects and the corresponding quantity in unexposed subjects) are used to evaluate the association between exposure and disease with a view to carry out etiological research, attributable risk is interpreted in public health as a measure of the fraction of the disease attributable to one (or more) exposure(s). Consequently, attributable risk is used to evaluate the potential impact of primary prevention programs aiming at eliminating exposure of a given population. It is often directly taken to be the fraction of the disease that might be eliminated if exposure of the population were to disappear totally.

However, such an interpretation can be misleading since to be accurate, the three following conditions must be fulfilled (Walter, 1976). First of all, the estimate of attributable risk must be free of bias (see below). Secondly, the exposure must be causal and not merely associated with the disease. Finally, elimination of exposure must have no effect on the distribution of other risk factors in the population. In fact, given the difficulty of modifying the level of exposure to an exposure factor independently of others, the change that results from elimination of one exposure factor in terms of presence of disease in the population may be different from the one measured by the attributable risk estimate calculation. As a result, various authors prefer to use more restrictive definitions of attributable risk such as the fraction of disease that can be linked or associated with rather than attributable to exposure.

A fundamental problem, which has to do with the nature of causality, has been discussed by Greenland and Robins (1988), Robins and Greenland (1989) as well as Rothman and Greenland (1998). These authors take into account the proportion of cases of the disease for which exposure has played an etiological role, i.e. cases for which exposure represents a causal factor of occurrence of the disease as opposed to cases for which exposure is merely present. They call this fraction the etiological fraction. Upon considering the causality models according to which several (and not just one) contributive causal factors must be present simultaneously or successively for the disease to occur, they show that the etiological fraction so defined differs from attributable risk and constitutes a more relevant measure of impact. Unfortunately, it is impossible in practice to distinguish among exposed cases those for which exposure has played an etiological role from those for which it has not. Consequently, the etiological fraction cannot be estimated in practice unless there are strong and generally unverifiable hypotheses on the mechanisms of action of the exposure factor and its interactions with other factors (Cox, 1984, 1985; Seiler, 1986; Robins and Greenland, 1989). In this context, attributable risk remains the most useful measure to evaluate the potential impact of exposure at the population level and can serve as a practical guide to evaluate and compare different strategies of primary prevention.

Fraction of disease explained by known factors

Several authors have considered interpreting attributable risk in terms of etiological research. According to this interpretation, if an estimate of attributable risk, AR, is available for several exposure factors jointly, it quantifies the fraction of disease etiology that can be explained, i.e. attributable (or at least linked) to such factors. Consequently, its complement to 1 (or 100%), 1-AR, must represent a measure of the proportion of cases of the disease that are not explained by such exposure factors and are thus attributable to other (possibly unknown) risk factors. For example, a 41% estimate of the attributable risk of breast cancer was reported for late first childbirth, nulliparity, family history of breast cancer and high socio-economic status. This suggests that 59% of breast cancer cases can be attributed to other risk factors (Madigan et al., 1995).

Similar reasoning lies behind several well-known publications that present the percentage of cancer deaths or incidents cases attributable to well-established preventable risk factors such as tobacco consumption, nutrition and occupational exposure to carcinogens. These publications convey the impression that only a small part of cancer deaths or cases remain to be explained by other factors than the main risk factors accessible to prevention and that cancer is therefore a disease that can essentially be prevented (Doll and Peto, 1981; Henderson et al., 1991; Ames et al., 1995; Colditz et al., 1996, 1997). Such an interpretation must be considered with caution since individual contributions of the various risk factors are not additive and their sum can be greater than 100% (see below) because of the possibility of multiple exposures (tobacco consumption and occupational exposure to asbestos, for

example). In addition, this interpretation may be questioned on the basis of causality models that consider several contributive factors (see below). Finally, it is worth noting that if we take into account a new risk factor on top of the ones that are already being considered, the reference category changes since it is then defined by the absence of exposure to the new factor and the factors previously considered (Begg, 2001). As a result of this change in reference category, the attributable risk for the new risk factor can be greater than the quantity 1-AR for the risk factors previously considered. Thus, if only 41% of breast cancers cases can be attributed to four established risk factors in the preceding example, it is quite conceivable that other risk factors for breast cancer might account for an attributable risk of over 59% in this example.

Properties

Two important properties of attributable risk deserve to be described: dependence on the definition of the reference level and distributivity.

Dependence on the definition of the reference level

The values of attributable risk strongly depend on the definition of the reference level for exposure. This level corresponds either to zero exposure or to an appropriate baseline level in case of an exposure continuum. A more restrictive definition of the reference level leads to a higher proportion of individuals being considered as exposed. Thus, the narrower the reference level by dropping the more exposed subjects (and therefore theoretically more at risk) from it, the higher the value of attributable risk. This property has a major impact on estimates of attributable risk as Benichou (1991) and Wacholder et al. (1994) have shown. For example, Benichou (1991) obtained an estimate of the risk of esophagus cancer attributable to alcohol consumption higher than or equal to 80 g/day (i.e. reference level of 0 to 79 g/day) of 38% for the Île-et-Vilaine department in France. This estimate went up to 70% for alcohol consumption higher than or equal to 40 g/day (using a reference level of 0 to 39 g/day). This property plays a role when studying a continuous exposure with a continuous risk gradient and no obvious threshold. Thus, estimates of attributable risk can be interpreted validly and make sense only by reference to a clearly defined baseline level.

The above estimates of attributable risk for esophagus cancer in Île-et-Vilaine were obtained from data of a case-control study carried out in the 1970's. This study included 200 cases of esophagus cancer and 775 controls selected on a random basis on the department's electoral listings (Tuyns et al., 1977). Assessment of the associations of alcohol consumption and smoking with esophagus cancer is illustrated in detail in a reference publication by Breslow and Day (1980) that presents several approaches to estimate the odds ratio with or without age adjustment. In the present illustration and in the course of previous work (Benichou, 1991), four levels of alcohol consumption (0-39, 40-79, 80-119 and ≥ 120 g/day), three levels of tobacco consumption (0-9, 10-29, ≥ 30 g/day) and three age groups (25-44, 45-54, ≥ 55) are being considered. There were 29, 75, 51 and 45 cases with a respective alcohol consumption of 0-39, 40-79, 80-119 and ≥ 120 g/day. The numbers of corresponding control subjects were 386, 280, 87 and 22 respectively.

The first reference level considered (0-79 g /day) includes 104 cases and 666 controls, which leaves 96 cases and 109 controls in the exposed category (≥ 80 g/day) (Table 8.I). The crude (i.e. non adjusted) odds ratio is equal to 5.6 (96×666/104×109). According to the methods described below, the crude attributable risk is estimated at 39.5% for alcohol consumption and about 38% after adjusting for age and tobacco consumption. The second reference level

considered (0-39 g/day) is more restrictive and only includes 29 cases and 286 controls, which leaves 171 cases and 489 controls in the exposed category (≥ 40 g/day) (Table 8.I). The corresponding crude odds ratio is estimated at 5.9 (171×386/29×389). According to the methods described below, the crude attributable risk is 70.9% and the adjusted attributable risk lies between 70 and 72%. This substantial increase results mainly from the higher proportion of exposed subjects with this more restrictive definition of the reference category (50% instead of 14% of exposed controls).

Table 8.I: Case-control study on esophagus cancer; numbers of cases and controls in the reference category and in the category exposed to daily alcohol consumption for two definitions of the reference category (from Tuyns et al., 1977)

More restrictive definition of the reference category (0-39 g/day)				Less restrictive definition of the reference category (0-79 g/day)		
	Reference (0-39 g/day)	Exposed (≥40 g/day)	Total	Reference (0-79 g/day)	Exposed (≥80 g/day)	Total
Cases	29	171	200	104	96	200
Controls	386	389	775	666	109	775
Total	415	560	975	770	205	975

Distributivity

The second important property of attributable risk is distributivity. If several exposed categories are being considered as opposed to one, then the sum of attributable risks for each exposed category is equal to the overall attributable risk calculated by combining the exposed categories into one irrespective of the dividing line chosen for the exposed categories, provided the reference category remains unchanged (Walter, 1976; Benichou, 1991; Wacholder et al., 1994). This property is strictly applicable to estimates of crude attributable risk and adjusted estimates calculated on the basis of a saturated model that includes all major effects and possible interactions (Benichou, 1991). It can be applied as an approximation for adjusted estimates that are not based on a saturated model (Wacholder et al., 1994). Thus if the overall estimate is the focus of interest, there is no need to divide the exposed category into several mutually exclusive sub-categories as a function of exposure level even in the presence of a risk gradient. However, if the issue of interest is the impact of partial exposure elimination, it will be necessary to use data pertaining to each exposed category (Greenland, 2001).

In the example above, the crude attributable risk is estimated at 79.9% for the definition of the most restrictive reference category of alcohol consumption (0-39 g/day). The separate contributions of the 40-79, 80-119 and ≥120 g/day categories are estimated at 27.0%, 22.2% and 21.7% respectively, which add up to the same value (70,9%) as when a single overall exposure category is being considered. Similarly, with the less restrictive definition of reference category of alcohol consumption (0-79 g/day), the crude attributable risk is estimated at 39.5% and the separate contributions of the 80-119 and ≥120 g/day categories are estimated at 18.7% and 20.8% respectively, which adds up to the same value (39.5%) as when a single overall exposure category is being considered.

Case of multiple exposure factors

Attributable risk is frequently estimated in multifactorial situations when trying to evaluate the joint and individual impact of multiple exposure factors associated with disease occurrence. This raises a problem since individual contributions of the factors to attributable risk are non-additive.

Non-additivity

When considering multiple exposure factors, it is possible to estimate distinct attributable risks for each exposure factor as well as an overall joint attributable risk for the various exposure factors. Walter (1983) has shown that the sum of risks attributable to each factor is not equal to the joint attributable risk unless two specific conditions are fulfilled: there is no joint exposure to the different exposure factors in the population (e.g. to tobacco and alcohol) and the effects of the exposure factors on disease risk are additive. For two exposure factors, the latter condition means that the relative risk for exposure to the two factors, RR_{12}, is linked to the relative risks for exposure to factors 1 and 2 separately, RR_1 and RR_2 respectively, by the formula $(RR_{12}-1)=(RR_1-1)+(RR_2-1)$. If none of the two conditions above are verified, then the sum of the risks attributable to each factor differs from the joint attributable risk and the difference can be substantial.

Table 8.II, taken from Begg (2001), illustrates this problem. The table considers two exposure factors E_1 and E_2 with a prevalence in the population of 0.25 for each of the joint exposure categories. Each of these exposure factors multiplies disease risk by 9 with a joint multiplicative effect such that the risk is multiplied by 81 in the case of joint exposure to both factors. By using either formula (1) or formula (2), one obtains an attributable risk of 80% for both factors E_1 and E_2 separately. Indeed, with formula (2) for example, the attributable risk for factor E_1 is:

$$AR_1 = 0.50 \times (9\text{-}1) \;/\; \{1 + 0.50 \times (9\text{-}1)\} = 0.80$$

i.e. AR_1=80%. The same applies to factor E_2 since the problem is perfectly symmetrical in this particular case. Thus the sum of the separate attributable risks for factors E_1 and E_2, i.e. $AR_1 + AR_2$, cannot be equal to the joint attributable risk for factors E_1 and E_2 since the sum is greater than 100%! The joint attributable risk for factors E_1 and E_2 can be obtained by using formula (1):

$$AR_{12} = \{Pr(D) - Pr(D \mid \bar{E})\} \;/\; Pr(D)$$

which is equivalent to:

$$AR_{12} = 1 - Pr(D \mid \bar{E}) \;/\; Pr(D)$$

where $Pr(D \mid \bar{E})$ is the risk of developing the disease in subjects that are neither exposed to E_1 nor E_2, i.e. 0.01. The probability $Pr(D)$ represents the risk of developing the disease in the population so that when the joint prevalence of exposure factors E_1 and E_2 are taken into account, the probability is:

$$Pr(D) = 0.25 \times (0.81 + 0.09 + 0.09 + 0.01) = 0.25$$

and, the joint attributable risk for factors E_1 and E_2 is:

$$AR_{12} = 1 - 0.01 \;/\; 0.25 = 0.96$$

i.e. AR_{12}=96%, which is clearly lower than the sum AR_1+AR_2. The non-additivity problem comes from the fact that by forming the sum AR_1+AR_2, one is not considering the same reference levels as when considering the joint attributable risk AR_{12}. For the latter, the reference level is the category that corresponds to an absence of exposure to E_1 and E_2. In the

case of the risk attributable to factor E_1, i.e. AR_1, the reference level corresponds to an absence of exposure to E_1 only and therefore includes subjects both exposed and unexposed to E_2 (in equal proportion in this example). Similarly, for the risk attributable to factor E_2, i.e. AR_2, the reference level corresponds to an absence of exposure to E_2 only and therefore includes subjects both exposed and unexposed to E_1 (in equal proportion in this example). This means that the contribution of the category of subjects exposed to both E_1 and E_2 is taken into account more than once in the sum AR_1+AR_2, which explains the inadequateness of calculating AR_1+AR_2 except in the specific cases described by Walter (1983).

Table 8.II: Illustration of the phenomenon of non-additivity of attributable risks for two exposure factors E_1 and E_2 and multiplicative risks

Exposure to factor E_1	Exposure to factor E_2	Prevalence	Relative risk	Risk	Risk in the absence of factor E_1	Risk in the absence of factor E_2
Yes	Yes	0.25	81	0.81	9	9
Yes	No	0.25	9	0.09	1	9
No	No	0.25	9	0.09	9	1
No	No	0.25	1	0.01	1	1

Solutions proposed – Sequential attributable risk

Because the non-additivity property is somewhat contrary to intuition and might engender erroneous interpretations, three alternative approaches have been suggested. The first approach is based on methods of variance decomposition (Begg et al., 1998) rather than estimating attributable risk and is therefore not directly applicable here. The second approach is based on estimating the probability of causation of each exposure, which is relevant in legal or compensation procedures where the aim is to determine the probability that the disease of a given individual having been exposed to several risk factors is due to one of these factors in particular, for example the probability that the lung cancer of a smoker occupationally exposed to asbestos is due to occupational exposure to asbestos (Cox 1984, 1985; Lagakos and Mosteller, 1986; Seiler, 1986; Seiler and Scott, 1987; Benichou, 1993; McElduff et al., 2002; Llorca and Delgado-Rodriguez, 2004). This approach being individual and non populational is not directly useable here.

The third approach is based on an extension of the concept of attributable risk (Eide and Gefeller 1995; Land et al., 2001) and is therefore more immediately relevant to the situation under consideration here. It relies on partition techniques (Land and Gefeller, 1997; Gefeller et al., 1998) and conserves the conceptual framework of attributable risk estimation while introducing the notion of sequential attributable risk, which generalizes the concept of attributable risk. The principle of this approach is to determine an order for the exposures under consideration. The contribution of each exposure is then evaluated sequentially according to its ranking. The contribution of the exposure that is placed first is calculated like the standard attributable risk for this exposure, were it separate. The contribution of the second exposure is obtained by calculating the difference between the joint attributable risk estimated for the first two exposures and the attributable risk estimated for the first exposure singly. Similarly the contribution of the third exposure is the difference between the joint attributable risk estimated for the first three exposures and the joint attributable risk for the first two exposures, etc… A multidimensional vector representing the contributions of each exposure is thus obtained.

Estimating these contributions is useful for potential prevention programs that consider the successive rather than simultaneous eliminations of exposures from the population. Thus, each step provides information about the additional effect of eliminating a given exposure after having eliminated the preceding exposures under consideration. After a certain number of steps, additional effects can become very small, thereby indicating that there are no reasons to consider additional steps. By construction, the sum of the contributions of each factor is equal to the joint attributable risk for all the exposures considered, which eliminates the problem of non-additivity. The contribution of each exposure factor depends on the order of the exposures considered. The most useful orders to consider depend on practical possibilities of implementation of potential prevention programs in a given population. Mean contributions, called partial attributable risks, can be obtained for each exposure factor by calculating the mean contribution for all the orders possible (Eide and Gefeller, 1995). Methods for visualizing sequential and partial attributable risks have been developed by Eide and Heuch (2001). These are illustrated in Figure 8.1. Land et al. (2001) present a detailed review of the properties and interpretation of sequential and partial attributable risks.

Taking once again cancer of the esophagus as an example, tobacco consumption is a well-known major risk factor for this cancer in addition to alcohol. It is therefore important to estimate the joint impact of tobacco and alcohol consumption on the occurrence of cancer of the esophagus relative to the impact of alcohol consumption alone. By using the first category (0-9 g/day) as the reference level category of tobacco consumption, we have 78 cases in the tobacco consumption reference level, 122 cases in the exposed category (i.e. ≥10 g/day), 447 controls in the reference category and 328 controls in the exposed category. From this data, the crude odds ratio for tobacco consumption of at least 10 g/day is estimated at 2.1 and the crude attributable risk at 32.4%. Since there are 9 cases and 252 controls in the category jointly exposed to tobacco and alcohol (0-39 g/day of alcohol and 0-9 g/day of tobacco), the crude joint odds ratio is estimated at 10.2 and the crude joint attributable risk for alcohol consumption of at least 40 g/day or tobacco consumption of at least 10 g/day is estimated at 86.2%.

Furthermore, the crude attributable risk for alcohol consumption of at least 40 g/day is estimated at 70.9% (see above). If one considers first the elimination of alcohol consumption of over 39 g/day, followed by the elimination of tobacco consumption of over 9 g/day, the sequential attributable risk is estimated at 70.9% for a high daily consumption of alcohol and 86.2–70.9=15.3% for substantial tobacco consumption, once daily alcohol consumption has been eliminated. The additional impact of eliminating substantial tobacco consumption therefore appears to be rather limited (Figure 8.1a). If we consider the other order possible, i.e. elimination of substantial tobacco consumption first, the sequential attributable risk is estimated at 32.4% for substantial tobacco consumption and 86.2-32.4=53.8% for high alcohol consumption once substantial tobacco consumption has been eliminated. Thus the major additional impact of eliminating the high daily consumption of alcohol remains (Figure 8.1b). These results are summarized by partial attributable risks for high alcohol consumption and substantial tobacco consumption of 62.4% and 23.9% respectively, which reflects the greater impact of alcohol consumption on the occurrence of esophagus cancer.

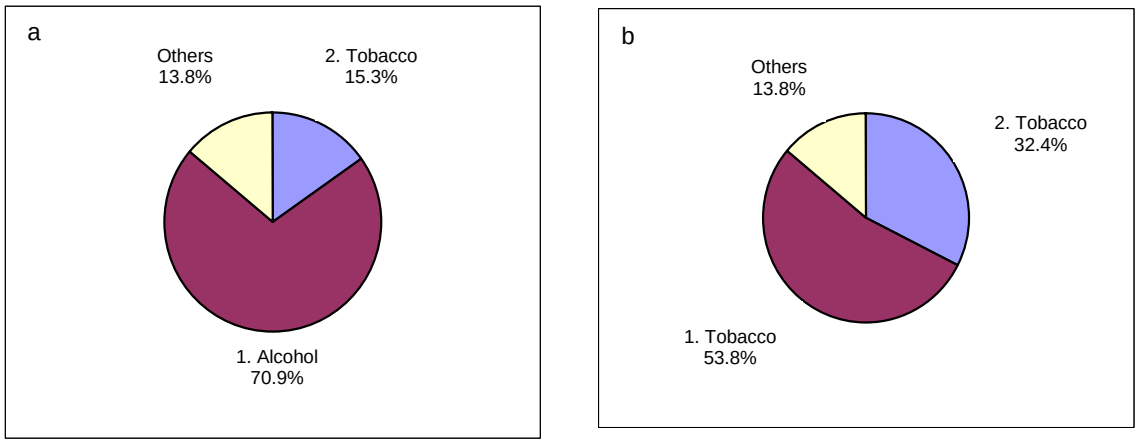

Figure 8.1: Sequential attributable risk for high alcohol consumption (>80 g/day) and substancial tobacco consumption (>10 g/day) depending on order of elimination (figure 8.1a: alcohol followed by tobacco; figure 8.1b: tobacco followed by alcohol). Case-control data on esophageal cancer (Tuyns, et al., 1977)

Estimating attributable risk

Attributable risk can be estimated from the main types of epidemiological studies.

Basic principles for estimating attributable risk

Attributable risk can be estimated from cohort studies since all the terms in formulae (1), (2) and (3) can be obtained directly from such studies. In case-control studies, risks or incidence rates specific for each exposure level are not available unless the data is complemented by follow-up or incidence data. One must therefore rely on odds ratio estimates, using formula (2), and estimate the prevalence of exposure in the population, p_E, from the proportion of exposed subjects among controls, by hypothesizing a rare disease (a hypothesis also used in odds ratio rather than relative risk estimation). In order to estimate crude attributable risks, the odds ratio is calculated with the formula ad/bc and p_E by $c/(c+d)$, where a, b, c and d are the numbers of exposed cases, unexposed cases, exposed controls and unexposed controls respectively. Alternatively, one can use formula (3), in which prevalence of exposure in subjects affected by the disease, $p_{E|D}$, can be directly estimated from the cases by the ratio $a/(a+b)$ and the relative risk by the odds ratio (ad/bc) as before. Whichever equation is used, the crude attributable risk estimate is finally obtained by the formula $(ad-bc)/\{d(a+b)\}$.

Estimators of variance are available that allow one to obtain confidence intervals for attributable risk. The respective merits of confidence intervals whether based or not on mathematical transformations (logarithmic or logistic) have been discussed in the literature (Walter, 1975, Leung and Kupper, 1981, Whittemore, 1982). Detailed reviews of the basic principles involved in the calculation of attributable risk for different types of epidemiological studies have been presented (Walter, 1976, Benichou, 2000a, 2001).

Taking once again the example of esophagus cancer with the most restrictive definition of the reference category of daily alcohol consumption (0-79 g/day), the crude attributable risk is calculated as follows:

$$(171\times386-29\times389)/(386\times200) = 0.709$$

i.e. 70.9% with a standard deviation of 0.051 or 5.1%. The corresponding 95% confidence intervals for attributable risk are [60.9-80.9%], [58.9-79.4%] and [60.0-79.8%] with no transformation, with the logarithmic transformation and logistic transformation respectively, thus giving three very similar results in this particular example.

Necessity of adjusted estimation

As with measures of association, crude (i.e. non adjusted) estimates of attributable risk can be invalid (Miettinen, 1974; Walter, 1976, 1980, 1983). The precise conditions under which the adjusted estimate of attributable risk, which takes into account the distribution and effects of other factors, is different from the crude estimate, which does not take them into account, have been determined by Walter (1980). If *E* and *X* are two dichotomous factors and if one wishes to calculate the attributable risk to exposure *E*, then the following result applies. The adjusted and non-adjusted estimates of attributable risk coincide (i.e. the crude attributable risk is not biased) if and only if (a) *E* and *X* are independent or (b) the exposure to *X* only does not increase the risk of disease occurrence. When considering one (or more) polytomous variables *X* with *J* levels (*J*>2), conditions (a) and (b) can be extended to a series of sufficient analogous conditions.

The extent of bias varies according to the degree of variation from conditions (a) and (b). Although there are to date no systematic numerical studies on crude (non-adjusted) attributable risk bias, Walter (1980) gives a revealing example of a case-control study that assessed the associations of alcohol and tobacco with oral cancer. In this study, substantial positive biases are observed for crude estimates of attributable risks, with a large difference between crude and adjusted estimates, both for tobacco consumption (51.3% *versus* 30.6%, an absolute difference of 20.7% and a relative difference of 68%) and alcohol consumption (52.2% *versus* 37.0%, an absolute difference of 15.2% and a relative difference of 48%).

It therefore seems essential to adjust for known or suspected confounding factors as one does when estimating measures of association. Furthermore, the non-adjusted estimates of attributable risk reported in the literature must be considered with caution.

Adjusted estimation – Stratification and regression methods

Several approaches have been proposed for adjusted AR estimation. The most general approach is based on the use of regression models. It relies on expressing attributable risk with the following formula (Bruzzi et al., 1985; Benichou, 1991):

$$\mathrm{AR} = 1 - \sum_{j=1}^{J} \sum_{i=0}^{I} \rho_{ij} RR_{i|j}^{-1}.$$

Each ρ_{ij} term represents the proportion of individuals with the disease (cases) with a level of exposure i (i=0 for the reference level, i=1,…, I for exposed levels) and a level of adjustment factor j (confounding factors). These terms can be calculated from cohort or case-control studies data by using the observed proportion of exposed subjects among cases. Each $RR_{i|j}^{-1}$ term represents the inverse of the relative risk, of the incidence rate ratio or of the odds ratio according to the context, for a level of exposure i at a given level j of adjustment factors. These terms can be calculated using regression models from cohort or case-control data. According to the type of study, Poisson or conditional or unconditional logistic regression models can be used. Thanks to these models, attributable risk calculations are adjusted for confounding factors and can also include terms representing the interaction between such confounding factors and the exposure factor(s) under consideration. Specific variance

estimators are available that allow calculation of confidence intervals for attributable risks (Benichou and Gail, 1989, 1990).

Such a regressional approach not only includes the non-adjusted approach as a specific case and the two adjusted approaches based on stratification methods but also offers additional options (Benichou, 1991). The non-adjusted approach corresponds to $RR_{i|j}^{-1}$ models that do not take confounding factors into account. Mantel-Haenszel's stratified approach (Greenland, 1984, 1987; Kuritz and Landis, 1987, 1988a, b) corresponds to models that include exposure and confounding factors but no terms to account for interaction between exposure and confounding factors. The weighted sum stratified approach (Walter, 1976; Whittemore, 1982, 1983) corresponds to saturated models where all the terms to account for possible interactions between exposure and confounding factors are included. Additionally, intermediate models can be considered that take into account the interaction between exposure and a single confounding factor (rather than all of them), or models in which the main effects of several confounding factors are not modeled by a saturated approach.

Coming back to the example of esophagus cancer with the most restrictive definition of the reference category for daily consumption of alcohol, an unconditional logistic model with two parameters, a general "intercept" parameter and a parameter for high alcohol consumption, can be used that does not take into account tobacco consumption or age. The calculated non-adjusted odds ratio is 5.9 as above. The formula given above for 1-AR is reduced in this case to a single two-term sum (i=0.1) corresponding to the unexposed and exposed categories. The non-adjusted attributable risk is estimated at 70.9% (with a standard variation of 5.1%), identical to the crude attributable risk calculated above. By adding eight terms for tobacco consumption and age in the logistic model, the adequateness of the model is significantly improved ($p<0.001$) and allows the calculation of an adjusted odds ratio of 6.3 and an adjusted attributable risk of 71.6% (with a standard variation of 5.0%), similar to what would be obtained with Mantel-Haenszel's stratification approach. By adding two terms for the interaction of tobacco and alcohol consumption, the attributable risk calculated is slightly lower (70.3% with a standard variation of 5.4%). Finally, by adding six more parameters that take into account one-to-one interactions of alcohol consumption with the joint level of tobacco consumption and age, one obtains a completely saturated model in which nine different odds ratios for alcohol consumption are calculated as in the weighted sum stratified approach. Thus the attributable risk is only slightly modified (with a value of 70.0%, identical to the value obtained with the weighted sum stratified approach, and a standard variation of 5.6%).

Detailed reviews on adjusted attributable risk estimation are available in the literature (Benichou, 1991, 2001; Gefeller, 1992; Coughlin et al., 1994).

Other measures of impact

Apart from attributable risk, other measures of impact have been proposed.

Preventable and prevented fractions

When considering a protective exposure or preventive intervention, an appropriate alternative to the attributable risk is the prevented or preventable fraction, PF, defined as the ratio (Miettinen, 1974):

$$PF = \{Pr(D \mid \overline{E}) - Pr(D)\} / Pr(D \mid \overline{E}) \quad (4)$$

where Pr(D) is the probability of occurrence of the disease in a population that comprises exposed (E) and unexposed individuals ($\overline{E}$), and Pr ($D \mid \overline{E}$) is the hypothetical probability of the disease in the same population if protective exposure were to be absent. According to the situation, such probabilities either refer to the risk or to the rate of disease incidence.

The prevented or preventive fraction PF can be written:

$$PF = p_E (1- RR) \quad (5)$$

which is a function of the prevalence of exposure, p_E, and the relative risk. Thus, as in the case of attributable risk, a strong association between exposure and disease can correspond to a high or low value of the prevented or preventive fraction PF since it is dependent on the prevalence of exposure. As a result, the PF fraction is not usually transposable from one population to another. Again as in the case of attributable risk, it can be useful to compare the estimated value for the PF fraction in different sub-groups of subjects in order to target prevention efforts on sub-groups for which impact is likely to be the greatest.

For a protective factor (RR<1), the value of the PF fraction lies between 0 and 1 and increases with the prevalence of exposure and strength of association between exposure and disease.

The PF fraction measures the impact of an association between a protective exposure and disease at the whole population level. Interpretation in terms of public health bears on the proportion of avoided cases (prevented fraction) thanks to the introduction of a protective exposure or preventive intervention in the population, among the totality of cases that would have arisen in the absence of such protective exposure or preventive intervention (*a posteriori* evaluation). Furthermore, it is possible to evaluate prevention programs *a priori* by measuring the proportion of cases that can potentially be avoided (preventable fraction) if a protective exposure or preventive intervention were introduced *de novo* in the population (Gargiullo et al., 1995). However, such interpretations are subject to the same limitations as interpretations of attributable risk.

Attributable risk AR and the PF fraction are mathematically interdependent (Walter, 1976) as shown in the equation:

$$1 - PF = 1 / (1 - AR) \quad (6)$$

This equation shows that, for a protective factor, the PF fraction generally differs from the attributable risk AR calculated by reversing the exposure coding. This is in agreement with the respective definitions of the AR and PF quantities. While the reverse coded attributable risk measures the potential reduction in the risk of disease occurrence were all the subjects in the population to become exposed, the PF fraction measures the reduction in the potential risk of disease occurrence that results from the introduction of exposure in a population that is initially not exposed (Bénichou, 2000b).

From equation (6), it becomes apparent that calculation of the PF fraction raises identical problems to those posed by attributable risk. In particular, methods of adjusted estimation based on Mantel-Haenszel's (Greenland, 1987) and weighted sum (Gargiullo et al., 1995) stratification approaches have been proposed.

Generalized impact fraction

The generalized impact fraction (GIF) or generalized attributable fraction has been defined by Walter (1980) and Morgenstern and Bursic (1982) as being the ratio:

$$GIF = \{Pr (D) - Pr^*(D)\} / Pr (D) \quad (7)$$

where the terms Pr (D) and Pr*(D) correspond to the probabilities of disease in the population for current and modified distributions of exposure respectively. As with

attributable risk and the prevented or preventable fraction, these probabilities can either describe the risk of the disease or its rate of incidence, according to the situation.

The generalized impact fraction not only depends on the association between exposure and disease and on the current distribution of exposure (rather than the sole prevalence of exposure), but also on the modified distribution $Pr^*(D)$ under consideration. It is therefore a general measure of impact that includes attributable risk and the PF fraction as specific cases. Attributable risk deals with the difference between the current distribution of exposure and a modified distribution defined by the absence of exposure. The PF fraction deals with the difference between a distribution defined by an absence of exposure and the current distribution of exposure in the population (prevented fraction) or an absence of current exposure and a target distribution of exposure (preventable fraction).

The generalized impact fraction can be interpreted as the fractional reduction of disease incidence that would result from a change in the current distribution to a modified distribution of exposure in the population. Thus, it is useful to evaluate prevention programs or interventions that target either all subjects or only subjects at specific levels of exposure and are aimed at modifying or reducing exposure without necessarily eliminating it totally. For example, some interventions might only focus on heavy rather than all smokers. The attributable risk corresponds to the specific case of exposure elimination by considering a modified distribution of exposure reduced to a single point, with all subjects becoming unexposed. Furthermore, the generalized impact fraction can be used to evaluate the increase in disease incidence that results from exposure modifications in a population, such as, for instance, the increase in breast cancer incidence resulting from late maternity in more recent age cohorts (Kleinbaum et al., 1982). The limitations of such interpretations are the same as for attributable risk and prevented and preventable fractions.

The generalized impact fraction has been used, for example, by Lubin and Boice (1989), who have measured the impact of a modification in radon exposure distribution on lung cancer by truncating the distribution according to different thresholds, and by Wahrendorf (1987), who examined the impact of various changes in nutritional habits on colorectal and stomach cancers.

The estimation problems and methods are similar to those that apply to attributable risk and the PF fraction. However, a possible difference lies in the necessity that might arise to consider the continuous nature of some exposures rather than rely on categories of exposure in order to define the modification of the distribution under scrutiny, e.g. an identical exposure reduction at each level (Benichou and Gail, 1990). Drescher and Becher (1997) have proposed an extension of the adjusted estimation approach based on regression models (Bruzzi et al., 1985; Greenland and Drescher, 1993) in order to estimate the generalized impact fraction in case-control studies and have considered continuous as well as categorical exposures.

Years of life lost

The number of years of life lost or potential years of life lost (PYLL) for a given cause of mortality is a measure defined by the difference between the current life expectancy of a population and the potential life expectancy after elimination of the cause of mortality (Smith, 1998). For instance, the PYLL due to prostate cancer in men, breast cancer in women or cancer in general in both sexes may be of interest. The methods for estimating PYLL figures are based on life table calculations. One can measure total PYLLs at the population level or mean PYLLs per individual. For example, the recent report from the American Surveillance, Epidemiology and End Results (SEER) network of registries estimates that 8.4

million life years have been lost owing to cancer in the United States population in 2001 (for both sexes and for all ethnical groups), with a mean of 15.1 years of life lost per individual. The corresponding figures are 779,900 years of life lost for breast cancer in women, i.e. a mean of 18.8 years per individual, and 275,200 years of life lost, i.e. a mean of 9.0 years per individual for prostate cancer in men (Ries et al., 2004).

PYLLs represent an evaluation of the impact of a given disease. They are therefore not directly interpretable as a measure of exposure impact, except perhaps for pathologies with a dominant risk factor, such as asbestos exposure in the case of mesothelioma, or papilloma virus for cancer of the cervix.

However, it is possible to obtain a corresponding measure of impact for a given exposure by converting PYLLs due to a specific cause of mortality into PYLLs due to a specific type of exposure (Robins and Greenland, 1991). The calculation of PYLLs linked to a given exposure is obtained by applying an estimated value for the risk attributable to this exposure to PYLLs linked to a specific disease, i.e. by calculating the product of PYLLs by the risk attributable to exposure. With this method, it is usually necessary to take several causes of mortality into account. For example, the contributions of mesothelioma and lung cancer need to be added in order to obtain the total PYLLs linked to occupational exposure to asbestos. As opposed to attributable risk, which measures the impact of exposure on disease incidence or mortality, PYLLs measures impact on a life expectancy scale. As with attributable risk, the impact of a given exposure as measured by PYLLs depends on the prevalence of exposure in the population and the strength of the association between exposure and disease. In addition, impact also depends strongly on the age distribution at which exposure-associated diseases occur as well as on associated mortality.

In conclusion, estimating the risk attributable to various environmental factors in the occurrence of cancers is undeniably helpful in defining priority measures for primary prevention in populations with a known prevalence of exposure. Because it integrates strength of association and prevalence of exposure in the population, attributable risk allows an evaluation and comparison of the potential impact of various primary prevention strategies.

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